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Editor
ROBERT J. BENFORD, M. D.
Colonel, Medical Corps
United States Air Force

Associate Editor
ROBERT S. ANDERSON, M. D.
Colonel, Medical Corps
United States Army

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Monthly Message

At the invitation of the Turkish Government, an Internation Nutrition Conference was held at Ankara on 14, 15, and 16 April 1958. The nations represented were Turkey, Iran, Pakistan, Iraq, and the United States. The United Kingdom had expected to send representatives but they were unavoidably detained. Libya had been invited to participate but was unable to send delegates.

This is the second internation conference of this sort, the first having been held in Tehran last year at the invitation of the Iranian Government. Dr. Arnold Schaefer, the Executive Director of the Interdepartmental Committee on Nutrition for National Defense, is the Secretary of these conferences and arrangements each year are carried through by him and the host country. Both deserve much credit for the consummation of these extremely successful conferences. This year there were excellent papers by all countries represented with free discussion, in fact so free that each day was not long enough.

The chairmanship rotated for each session as did the temporary secretary so that all countries had the opportunity to conduct the meetings. In all probability next year's session will be held in Pakistan where we can look forward to an equally good program because of the interest manifested in that country. Although the principal purpose of these meetings is the improvement of nutrition in the armed forces, nevertheless interest soon spreads to the civilian groups. There is close cooperation throughout with our own International Cooperation Administration programs to assist materially in establishing food processing factories and providing instruction and advice for their management.

Frank B. Berry

FRANK B. BERRY, M. D.
Assistant Secretary of Defense
(Health and Medical)

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Foreword

The *United States Armed Forces Medical Journal* is the medium for disseminating information of administrative and professional interest to all medical personnel of the Department of Defense. The Assistant Secretary of Defense (Health and Medical) and the Surgeons General of the several services invite all medical officers, dental officers, Medical Service Corps officers, Nurse Corps officers, and officers of the Veterinary Corps of the Armed Forces, and the medical consultants of the Army, Navy, and Air Force to submit manuscripts for publication in this *Journal*.

FRANK B. BERRY, M. D.,
Assistant Secretary of Defense (Health and Medical).

MAJOR GENERAL SILAS B. HAYS,
Surgeon General, United States Army.

REAR ADMIRAL BARTHOLOMEW W. HOGAN,
Surgeon General, United States Navy.

MAJOR GENERAL DAN C. OGLE,
Surgeon General, United States Air Force.

UNITED STATES ARMED FORCES MEDICAL JOURNAL

Volume IX October 1958 Number 10

REVISED DEPENDENTS' MEDICARE PROGRAM

FRANK B. BERRY, *M. D.*

IN order that all members of the uniformed services, especially physicians, will be adequately informed about the major changes in the Medicare Program as a result of Congressional action, effective 1 October 1958, it is important that the basic facts pertaining to these changes be made known through the *Journal*.

It is essential that the restrictions as to freedom of choice, imposed on spouses and children of active-duty service personnel, and the reductions in authorized medical care be thoroughly familiar to those who are concerned in providing the medical care for dependents in service medical facilities. Unless this knowledge is available and known by our medical personnel, it may well complicate the administrative problems attendant to dependents seeking such care from civilian facilities.

It must be remembered:

Written permission to obtain civilian medical care must be obtained only by those dependents residing with their sponsors or in an area in which the sponsor is assigned.

The reduction in authorized care involves all dependents, not only those residing with their sponsors, but also those residing apart from their sponsors.

All medical officers should study carefully the changes in authorized care. Both of the above restrictions will divert dependents seeking medical care to service medical facilities. Every consideration to good physician-patient relationship should

Dr. Berry is the Assistant Secretary of Defense (Health and Medical), Department of Defense, Washington, D. C.

be encouraged. Everyone in the treatment facility dealing with these dependents—from the receptionist to the laboratory technician, and especially all attendants—should be friendly, courteous, considerate, and helpful to such patients.

The information included herein should be read and understood by everyone concerned with medical care of dependents of service personnel on active duty. To do so will help retain high morale, as well as to provide optimum utilization of our uniformed services' medical facilities.

The changes in the Medicare Program effective 1 October 1958 fall into two broad categories: (1) Restrictions on the use of civilian medical facilities for dependents residing with the service member on whom they are dependent; and (2) Reductions of the authorized care and services provided from civilian sources for which the Government will pay.

To see precisely what dependents of members of the uniformed services may expect under the revised program, let us examine the program in detail.

ELIGIBILITY FOR CIVILIAN MEDICAL CARE

Some dependents are eligible for both civilian medical care and care in service facilities. For a dependent to be eligible, the sponsor must be on active duty, or on active duty for training, for a period of more than 30 consecutive days. The dependent must also bear one of the following relationships to the sponsor:

Lawful wife.

Lawful husband, if dependent on service wife for over one half of his support.

Unmarried legitimate child, adopted child, or stepchild, in one of the following categories: (1) Under 21 years of age; (2) over 21, but incapable of self-support because of mental or physical incapacity that existed before the age of 21, and dependent on service member for over one half of support; or (3) under 23, enrolled in a full-time course in an approved institution of higher learning, and dependent on service member for over one half of support.

Eligibility of the dependent for civilian medical care ceases when the service member who is the sponsor dies, is discharged, divorced, retires, or is released from active duty. Eligibility also ends if the sponsor is dropped from the rolls of his service in desertion. If he dies while on active duty or while in a retired status, his dependents are still eligible for care at Armed Forces and U. S. Public Health Service medical facilities when space and staff are available.

For purpose of administering the revised Medicare Program, dependents who meet the above requirements are divided into two classes:

1. Dependents residing *apart* from sponsors.
2. Dependents residing *with* sponsors.

How does the revised Medicare Program affect each of these classes?

Dependents Residing Apart from Sponsors. Dependents eligible for civilian medical care who reside apart from their sponsors may continue to choose between civilian facilities or a facility of the Armed Forces, or they may use a U. S. Public Health Service medical facility.

Civilian physicians and hospitals, when providing care for dependents, will each furnish the dependent with a claim form (DA Form 1863 entitled "Statement of Services Provided by Civilian Medical Sources"), to be filled in. When the dependent patient resides apart from the sponsor, item 4 on the claim form must indicate that the patient is residing apart from sponsor. If the attending physician requires the services of other physicians, an anesthetist, or a private-duty nurse while the dependent patient is in a civilian hospital, a DA Form 1863 must be completed for each of them. These claim forms also must indicate that the patient resides apart from sponsor.

When applying for civilian medical care, the dependent should first ask the physician if he will participate in the Medicare Program.

Dependents Residing With Sponsors. Wives and dependent husbands and children of service members, who reside with their sponsors, are required to ascertain from a uniformed service's authority whether the required care can be provided in a nearby service medical facility.

When the authorized care is *not* available from service medical facilities, the dependent must get a Medicare Permit (fig. 1) from the appropriate service authority to seek authorized civilian care. This permit allows the dependent to receive care authorized under the revised Medicare Program from civilian sources at Government expense and is for immediate use.

In some cases, Government-paid medical care from civilian sources may be provided without a Medicare Permit. These are as follows:

1. In an acute emergency requiring immediate hospitalization at the nearest hospital in order to preserve life and prevent undue suffering. The attending physician must state on the claim form (DA Form 1863), or on an attachment to the claim form, that the case is actually an acute emergency.

2. When the dependent is away from the area of the sponsor's household on a trip, the person signing item 14 on the claim will be required to make an entry in item 3 or 4 certifying that the dependent is "on

trip." This exception is not to be used to circumvent restrictions in the new Medicare Program.

MEDICARE PERMIT
(AR 40-121, SECNAV INST 6320.8, AFR 160-41, PHS GEN CIR NO 6)

THIS PERMIT IS ISSUED FOR IMMEDIATE USE AND WHEN PRESENTED WITH THE UNIFORMED SERVICES IDENTIFICATION AND PRIVILEGE CARD (DD FORM 1173) IDENTIFIED BELOW, ALLOWS THE DEPENDENT NAMED BELOW WHO IS RESIDING WITH SPONSOR TO OBTAIN CIVILIAN MEDICAL CARE UNDER THE DEPENDENTS' MEDICAL CARE PROGRAM IF SUCH CARE IS AUTHORIZED FROM CIVILIAN SOURCES UNDER THE PROVISIONS OF THE DEPENDENTS' MEDICAL CARE ACT (P. L. 569, 84TH CONGRESS; 70 STAT. 250-253) AND REGULATIONS ISSUED THEREUNDER. THIS PERMIT DOES NOT RENDER THE GOVERNMENT RESPONSIBLE FOR PAYING FOR CARE WHICH IS NOT AUTHORIZED (SEE EXAMPLES BELOW) TO BE OBTAINED FROM CIVILIAN SOURCES UNDER SAID ACT AND REGULATIONS, AND ITS USE IS SUBJECT TO THE CONDITIONS AND LIMITATIONS SET FORTH IN SAID REGULATIONS.

DEPENDENT, SPOUSE OR CHILD, RESIDING WITH SPONSOR

DEPENDENT'S LAST NAME - FIRST NAME - MIDDLE INITIAL	AGE	RELATIONSHIP TO MEMBER OF UNIFORMED SERVICES
JONES, Mary Margaret	28	[X] WIFE [ ] HUSBAND [ ] DAUGHTER [ ] SON

DEPENDENT'S ADDRESS (COMPLETE MAILING ADDRESS)	IF CHILD OVER 21, DEPENDENCY CAUSED BY
1418 Elm Street Bigtown, Virginia	[ ] MENTAL AND/OR PHYSICAL HANDICAPS [ ] ENROLLMENT IN EDUCATIONAL INSTITUTION

UNIFORMED SERVICES IDENTIFICATION AND PRIVILEGE CARD (DD FORM 1173)

CARD NUMBER			EXPIRATION DATE
PREFIX	NUMERICAL	SUFFIX	
AA	12,498	A	31 Dec 1962

SPONSOR MEMBER OF UNIFORMED SERVICES ON ACTIVE DUTY

SPONSOR'S LAST NAME - FIRST NAME - MIDDLE INITIAL		BRANCH OF SERVICE
JONES, James W.		[X] ARMY [ ] NAVY
SERVICE NUMBER	GRADE OR RANK	[ ] AIR FORCE [ ] COAST GUARD
RA 1,234,567	Master Sergeant	[ ] MARINE CORPS [ ] PUBLIC HEALTH
		[ ] COAST AND GEODETIC SURVEY

ORGANIZATION AND OFFICIAL DUTY STATION
101 Engineer Battalion, Fort Blank, Virginia

REMARKS

STATION AT WHICH PERMIT ISSUED	DATE ISSUED
Fort Blank, Virginia	15 October 1958

GRADE OR RANK, AND POSITION OF ISSUING OFFICER	SIGNATURE OF ISSUING OFFICER
John D. Doe, Captain, AGC Adjutant	John D. Doe

EXAMPLES OF CARE NOT AUTHORIZED

1. OUTPATIENT CARE AND/OR SERVICE PER SE OF ANY NATURE EXCEPT MATERNITY CARE AND DIRECT COMPLICATIONS THEREOF.
2. NERVOUS AND MENTAL DISEASES (ACUTE EMOTIONAL DISORDERS).
3. PLANABLE SURGERY. EXAMPLES OF WHICH ARE TONSILLECTOMY, COSMETIC SURGERY, HYSTERECTOMY (ROUTINE), HEART SURGERY, RHINOPLASTY AND RECONSTRUCTIVE ORTHOPEDIC AND PLASTIC PROCEDURES.

DD FORM 1251
1 XXX 58

Figure 1. New Medicare Permit.

3. A maternity patient (residing with sponsor) under the care of a civilian physician on or before 1 October 1958 may continue under his care *provided* the patient has reached the 15th week of pregnancy on or before that date. The attending physician will indicate on DA Form 1863 (or attachment to it) that the patient meets the above requirements. The hospital will also make a similar statement on its DA Form 1863.

4. In the case of a dependent who was admitted to a civilian hospital before 2400 hours, 30 September 1958, when the hospital care required for this admission extends beyond 30 September 1958. The date of

admission shown by the hospital on the claim form must indicate that the admission occurred before 1 October 1958.

5. When a dependent is receiving authorized care from a physician and is admitted to a civilian hospital before 2400 hours, 30 September 1958, the dependent will be authorized such care by that civilian physician. On the claim form the physician must show that the date of admission to the civilian hospital was before 1 October 1958.

CIVILIAN CARE PROVIDED

Effective 1 October 1958, the Government pays the major cost of the following services for those eligible dependents who meet the requirements for civilian medical care:

Hospitalization in semiprivate accommodations (2, 3, or 4 beds), not to exceed 365 days for each admission, and the physicians' bills during hospitalization for treatment of: (1) acute medical conditions; (2) contagious diseases; (3) surgical emergencies; (4) acute surgical conditions; and (5) severe injuries, during the acute phase.

Laboratory and x-ray tests and procedures during hospitalization.

Complete obstetrical and maternity care, including in-hospital care of the newborn infant. Infants delivered by civilian physicians in a home or an office may receive required authorized care on an outpatient basis during a period not to exceed 10 days following the date of delivery.

CIVILIAN MEDICAL CARE NOT PROVIDED

Effective 1 October 1958, the following care and services are not authorized from civilian sources:

1. Treatment of fractures, dislocations, lacerations, and other wounds not requiring hospitalization.

2. One visit to a civilian physician, whose services terminate before or upon hospitalization of the patient.

3. Pre- and post-surgical tests and procedures, such as roentgenograms, and laboratory tests performed on an outpatient basis except in maternity cases.

4. Two visits by a physician to examine an infant within 60 days after birth. The hospital care of a newborn infant is still provided as part of complete maternity care.

5. Treatment of acute emotional disorders. Care of an acute emotional disorder may be furnished to a spouse or child, however, if required, but only during the period of hospitalization of that spouse or child for a condition that *does* qualify as authorized care.

6. Medical and surgical care that can be planned. Medical or surgical care that is desired or requested by the patient which, in the opinion of the responsible medical authority, can be planned, later scheduled, and effectively treated at a later date without detriment to the patient.

Examples are: diagnostic surveys, cosmetic surgery, reconstructive surgery, tonsillectomies, uncomplicated hernias, operations for relieving or producing sterility, and appendectomies when not an acute surgical problem.

7. Chronic disease, except for acute exacerbations or acute complications requiring treatment in a hospital.

8. Domiciliary care. This means personal nursing care normally provided in an institution, such as a nursing or convalescent home.

9. Ambulance service. (May be provided by service facilities under limited circumstances.)

10. Medical supports or aids. Dependents who need a prosthesis, hearing aid, orthopedic footwear, or spectacles will have to buy them at their own expense. Outside continental United States or in a prescribed remote area within the United States, where such appliances are not available from private sources, such items may be sold to dependents, if available, from Government stocks at cost.

CIVILIAN OUTPATIENT CARE

Outpatient care from civilian sources is restricted to authorized obstetrical and maternity care. For all other outpatient care at Government expense, dependents must use uniformed services medical facilities.

DENTAL CARE

The provisions for dental care remain unchanged. Generally, the Government will not pay for civilian dental care. Dental treatment is provided only to patients, who are hospitalized for otherwise authorized care, as a necessary part of the treatment of the basic medical or surgical condition requiring their hospitalization. It does not include the cost of artificial teeth, bridges, fillings, teeth straightening, or prolonged treatment of the gums.

At Armed Forces and U. S. Public Health Service medical facilities, dental care is provided as follows:

In continental United States:

1. In an emergency, to relieve pain and undue suffering. Permanent fillings, bridges and dentures, are *not* authorized.
2. If required for treatment of a medical or surgical condition.
3. Dental care in areas designated "remote" on a facilities-available basis.

Outside continental United States:

1. Dental care on a facilities-available basis.

CARE IN SERVICE MEDICAL FACILITIES

If medical staff, space, and facilities are available, the medical services of the uniformed services will provide care for all eligible dependents as follows:

Diagnosis.
Treatment of:

1. Acute medical conditions.
2. Surgical conditions.
3. Contagious diseases.
4. Acute emergencies of any nature.

Immunization.
Maternity and infant care.

MEDICAL CARE OVERSEAS

As a general rule, dependents will receive required care from service medical facilities when they are outside continental United States, Alaska, Hawaii, and Puerto Rico. If Armed Forces or U. S. Public Health Service facilities are lacking or inadequate, civilian medical care may be arranged for at the expense of the U. S. Government. Dependents residing in oversea areas where service medical care cannot be provided may obtain full information from the appropriate oversea commander or from the nearest service installation on how to obtain medical care from professionally acceptable local civilian sources.

ELIGIBILITY FOR MILITARY CARE

Dependents are eligible for care in service medical facilities if they bear one of these relationships to a retired service member, to a service member who died while serving on active duty for a period of more than 30 days, or to a deceased retired service member:

Lawful wife.
Lawful husband, if dependent.
Unremarried widow.
Unremarried widower, if dependent.
Unmarried legitimate child, adopted child, or stepchild if such child has not passed his 21st birthday. See page 1406 for exceptions covering those past 21 years of age.

Parent or parent-in-law, if dependent and if residing in a dwelling place provided or maintained by the service member or retired service member. (A parent or parent-in-law of an active-duty service member is also qualified for care at service facilities if he meets the above requirements.)

IDENTIFICATION

When applying for any kind of medical care to a service or civilian facility, or to a civilian physician, dependents are required to present a Uniformed Services Identification and Privilege Card (DD Form 1173) as proof of eligibility for medical care.

All eligible dependents except children under 10 years of age may obtain a card. In some cases, such as a child living apart from his parents, a card may be issued even for a child under 10. In the case of a child under 10 the parent or guardian must furnish proper identification and certify as to the child's eligibility.

Dependents residing with their sponsors will receive their cards through their sponsors. The sponsor will fill out the necessary application form and submit it to his commanding officer. Sponsors residing apart from their dependents may send the completed application form to their dependents.

If the sponsor is unable, or declines, to fill out the application form, his dependent can obtain the necessary application form at any service installation, fill in as much information as possible, and submit it to the sponsor's commanding officer for completion and verification.

Dependents of service members who died while on active duty or while in a retired status may obtain an application for the card from a nearby service facility by applying there in person or requesting it by mail. Information on how to fill out the form and what certificates must accompany it can be obtained at the same time.

The completed application form must be taken to a uniformed service facility. If the necessary equipment to produce the card is not available there, the dependent will be advised where to obtain the card. Dependents who cannot visit a service facility that can issue the card may request it by mail.

The card must be turned in (1) when it expires; (2) when a new card is issued; (3) when the sponsor dies, is discharged, retires, or is released from active duty; or (4) when the dependency status is otherwise ended. When a card is lost, the loss should be reported immediately, so it may be replaced and the services may be on the alert against its being used improperly by someone who finds it.

If a person uses a card to obtain medical care to which he is not entitled, a fine of up to $10,000 and imprisonment for up to 5 years may be imposed on the offender. A dependent who allows another person to use his card unlawfully may be subject to the same penalties. Damage to, or indications of tampering with, the laminated card makes it invalid.

A WORD OF CAUTION

Dependents residing with their sponsors, in addition to furnishing proper identification, must present a Medicare Permit to the source of civilian care except under those circumstances previously stated.

Except in an emergency, eligible dependents seeking medical care from civilian sources should make sure the physician and hospital are participating in the Medicare Program before beginning treatment.

A physician participating in the program must be legally licensed and qualified to prescribe and administer all drugs, and to perform all surgical procedures.

A hospital, to qualify under the Medicare Program, except in an emergency, must be engaged primarily in providing facilities for the surgical and medical diagnosis, treatment, and care of injured and sick persons by or under the supervision of two or more staff physicians or surgeons. It must also provide continuous 24-hour nursing service by registered graduate nurses.

THE SHOTGUN CAPSULE

A few decades ago, before medicine became as precise and scientific as it is today, doctors' prescriptions often consisted of six to eight or more ingredients, many of which were more or less inert. The prescriptions were written in Latin, and the mystery of the ingredients constituted part of their virtue. Gradually, most of this sort of unscientific and meaningless procedure was abandoned; professors of medicine and of pharmacology taught students to use simple drugs, for precise reasons and for definite periods. Gradually, with the intense development of chemotherapy, of antibiotic therapy, of antihistaminic therapy, of endocrinologic therapy and of vitamin therapy there has been a mushrooming of drug manufacturers who are in desperate competition. The commercialistic factor has crept into therapeutics to such an extent that physicians everywhere are confused and misled by the literally thousands of drugs increasing in number daily. Dozens of expensive commercial brochures, sample drugs and elegant preparations reach one's office daily and are promptly disposed of in the wastebasket. Many of these modern preparations are mixtures of drugs, some of which are dangerous, some of which are useless, and most of which would be more intelligently given as separate drugs rather than in a shotgun capsule.

—CLAUDE E. FORKNER, M. D.
in *The New England Journal of Medicine*
p. 439, Aug. 28, 1958

ESSENTIAL HYPERLIPEMIA

GEORGE E. GORSUCH, *Lieutenant, MC, USN*

THE clinical condition manifested by an idiopathic familial hypertriglyceremia with varying levels of blood cholesterol and phospholipids is called essential hyperlipemia. The characteristic laboratory feature in this disease is milky white serum in the fasting state. In 1932, Bürger and Grütz[1] described hyperlipemia, hepatosplenomegaly, and xanthomatous eruption in a 12-year-old boy, believed by many to be the first reported case of essential or idiopathic hyperlipemia. The condition has been separated into a familial childhood type associated with hepatosplenomegaly and abdominal pain, and a nonfamilial variety which frequently was without symptoms and sometimes associated with glycosuria.[2] This division is somewhat untenable at present, and most authors now consider all forms simply as idiopathic or essential hyperlipemia. Over seventy cases have been noted thus far in the literature.[3-15] The syndrome of a classical case of essential hyperlipemia includes (1) opaque, white serum in the fasting state; (2) a family history; (3) recurrent abdominal pain; (4) lipemia retinalis; (5) hepatosplenomegaly; (6) xanthoma of the skin; and (7) an absence of other known causes of hypertriglyceremia.

The following case of essential hyperlipemia was observed for an 11-year period.

CASE REPORT

A 40-year-old Caucasian was admitted to this hospital on 24 April 1957 for evaluation of a blood pressure of 170/90 mm Hg and albuminuria, which had been discovered during a routine physical examination.

Past history revealed that the patient had been in good health until sometime in 1946, at the age of 30 years. He was on active duty in the Navy when he sustained an episode of severe abdominal pain, back pain, chills, fever, nausea, and vomiting. He eventually was hospitalized for 5 days at the U. S. Naval Hospital, Newport, R. I., where no definite diagnosis was established. He was readmitted to that hospital the later part of 1947 because of complaints of chest pain, fatigability, and hot flashes. He had transient hypertension and albuminuria at that time. No diagnosis was established and the patient was again

From U. S. Naval Hospital, San Diego, Calif. Dr. Gorsuch is now assigned to U. S. Naval Hospital, Bethesda, Md.

discharged to full duty. He continued to have intermittent abdominal pain and "stomach" distress.

In February 1948, the patient consulted his family physician. A blood sample, drawn at that time, was "milky," and a biopsy performed on a lump found on the back of the patient's neck was reported as showing "benign fat necrosis."

In June 1948 this man was again admitted to the U. S. Naval Hospital, Newport, R. I., because of abdominal pain. A laparotomy was performed, and the peritoneal cavity was noted to be full of milky-white fluid. No other definite pathologic condition was described on the operative note. The incision was closed quickly because of deterioration of the patient's condition on the operating table. A blood sample taken during that admission was milky white, and the previously noted history of milky serum was then disclosed to the attending physicians. A sample of blood was sent to the laboratories of Dr. S. J. Thannhauser, and a report on this blood was as follows: Total fatty acids, 6,785 mg per 100 ml; neutral fats, 5,665 mg per 100 ml; total phospholipids, 771 mg per 100 ml; total cholesterol, 1,170 mg per 100 ml; free cholesterol, 256 mg per 100 ml; cholesterol as esters, 828 mg per 100 ml. The patient's clinical course and laboratory findings were said to be typical of the picture of idiopathic hyperlipemia. This patient was again discharged to duty on a low-fat diet. He continued to have recurrent episodes of abdominal pain. In 1949 he was re-evaluated at the U. S. Naval Hospital, Chelsea, Mass., where his serum was again noted to be milky.

In April of 1952 he was admitted to U. S. Naval Hospital, Portsmouth, Va., in an acutely ill condition. He complained of severe generalized abdominal pain, nausea, vomiting, and back pain. A serum amylase on that admission was reported as normal. Because of the patient's past history, he was treated as having acute pancreatitis associated with essential hyperlipemia. He responded very well. When this patient's acute episode subsided and he was able to relax sufficiently, a large mass was palpated in the right upper quadrant of his abdomen. At exploratory laparotomy a large pseudocyst of the pancreas was found and drained. The gallbladder contained many yellow cholesterol stones, and it also was removed. The patient apparently recovered fully and was returned to duty. He remained well and had no symptoms referable either to hyperlipemia or pancreatitis. Slight albuminuria had been noted in 1954. In 1955 he was hospitalized for labile hypertension at the U. S. Naval Hospital, Newport, R. I., for three days.

There was no family history of diabetes. The patient's father died of heart trouble at the age of 70 years, and his mother died following a "ruptured appendix," at the age of 35. The two brothers and one sister were living and well, with ages ranging from 33 to 44 years. One brother had had a "ruptured appendix." One brother had "hyperlipemia and hypercholesteremia." All grandparents were over the age of 65 years at the time of their death, and there was no family

history of xanthomatosis and no other history of xanthomatosis except as noted in the previous (February 1948) biopsy report.

On the present admission, system review revealed that the patient rarely ate fatty food, but had no marked intolerance to it. His stools were normal in size, color, and consistency. There was no history of kidney disease except the previously noted albuminuria. There was no history of heavy alcohol intake.

Physical examination on admission revealed an obese, sluggish-appearing man with a florid complexion, who did not appear acutely or chronically ill. His blood pressure was 130/80 mm Hg. His weight was 225 pounds. A funduscopic examination was negative. There was no evidence of lipemia retinalis, and there were no hypertensive or arteriosclerotic changes. No xanthoma was found on examination of the skin. The spleen was firm and easily palpable three fingersbreadth below the left costal margin. The liver also was firm and nontender four fingersbreadth below the right costal margin. The remainder of the physical examination was entirely negative.

Laboratory studies on admission revealed the following: Serum lipemia was 4 plus. The serum was creamy white. Total lipids, 3,550 mg per 100 ml; phospholipids, 63.4 mg per 100 ml; total cholesterol, 684 mg per 100 ml; cholesterol as esters, 410 mg per 100 ml. Thyroid function tests were within normal limits. Total protein was 12.1 grams (albumin 5.3 grams, and globulin 6.8 grams) per 100 ml. An electrophoretic serum study revealed mild reversal of the albumin to globulin ratio with an increase in the beta fraction, presumably reflecting an increase in the beta lipoproteins. Serial urinalysis revealed negative urines except for an occasional specimen which contained 10-30 mg of albumin per 100 ml. Other laboratory studies or findings which proved to be negative or within normal limits included blood cell counts, serologic tests for syphilis, blood urea nitrogen, glucose tolerance test, serum amylase study, stool smears for undigested fat (sudan III), electrocardiogram, intravenous pyelogram, roentgenogram of the chest, a flat film of the abdomen, Bence Jones protein test, urinary concentration and dilution test, urine culture, Addis count, phenolsulfonphthalein test, and a battery of liver function tests. A serum lipase study was reported as showing no activity.

This patient's course in the hospital was uneventful. He demonstrated no hypertension. No definite cause was found for his mild intermittent albuminuria. He was placed on a rigid low-fat diet (20 grams) and at the end of two weeks, his total lipids dropped to 1,500 mg per 100 ml and his blood cholesterol fell to 522 mg per 100 ml. The patient was then placed on a sitosterol preparation in doses of 1 tablespoon, three times each day, before meals. The patient's last recorded blood cholesterol on this admission was 330 mg per 100 ml with 209 mg per 100 ml of cholesterol as esters. Repeated blood lipid studies were not reported by the day of discharge of this man. The patient's weight on discharge was 202 pounds. It was thought that his therapy was satisfactory, and he was discharged to duty and

retirement. When the patient was seen on an outpatient basis on 26 August 1957, he was asymptomatic and well. He weighed 195 pounds. His nonfasting serum was turbid but not milky. His blood cholesterol was 296 per 100 ml with 224 mg per 100 ml as esters. A pyridoxine-unsaturated fatty acid preparation was added to his therapeutic regimen.

DISCUSSION

Essential hyperlipemia involves a defect in blood lipid regulation, and any comments on this disease should include some remarks concerning the state of blood lipids and basic definitions. The blood lipids include the triglycerides or neutral fats, the phospholipids, and cholesterol. Most of the blood lipids are closely associated with the alpha and beta globulins in the form of lipoprotein complexes. The so-called beta lipoproteins are rich in fat and relatively low in protein and have been incriminated in the genesis of atherosclerosis. The serum lipoproteins also have been characterized by ultracentrifugal technics. With this technic, the rate of upward migration of a lipoprotein molecule under certain specific conditions has been expressed as Svedberg flotation units (S_f).[16, 17] An increase in the S_f number indicates an increase in the molecular lipid content, the size of the lipoprotein molecule, and a decrease in molecular density. The major cholesterol- and phospholipid-bearing molecules are in the groups S_f 17 and lower.[17] The S_f 100-S_f 400 class and above to 40,000 are composed mainly of neutral fats and only small amounts of proteins, cholesterol, and phospholipids.[18] A total cholesterol reflects the sum of the contributions of cholesterol from all members of the lipoprotein spectrum.[19] It has been reported that the incidence of atherosclerosis is correlated with increases of certain classes of the lipoprotein spectrum.

Although it has been suggested that the term "hyperlipemia" be used exclusively to indicate an increase in the neutral fat fraction of the blood lipids,[2] it has become increasingly difficult to do so without qualification. Following the example of Zilversmit,[20] the term "hypertriglyceremia" has been used in this writing to indicate an increase in the blood neutral fats. Hyperlipemia is utilized as a less specific term to indicate an increase in more than one fraction of the blood lipids with the implication that the blood neutral fats is one of these fractions. Hypertriglyceremia is frequently associated with hyperlecithemia and hypercholesteremia, though either of the latter two conditions may exist without an increase in the blood neutral fats.[21] Alimentary hyperlipemia is a postabsorptive phenomenon in which an increase in the blood neutral fats follows a fatty meal. The phospholipids and cholesterol may increase somewhat in the postabsorptive state, though not to the same degree as the neutral fats and this is variable. A sufficiently high concentration of neutral fat or very low-density lipoprotein

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molecules in aggregates or particulate form will render the blood serum milky white and impervious to light.[3, 18, 22, 23] This appearance of the serum is called lactescence and is known to occur in diabetic acidosis, nephrosis, acute pancreatitis, von Gierke's disease, and essential hyperlipemia.[2, 22] Lactescent serum is not ordinarily found in diabetes mellitus, biliary obstruction, or hypothyroidism, although hypercholesteremia is frequently present in these diseases.

Clinical Features

Appearance of serum and lipoprotein pattern. The case of essential hyperlipemia demonstrated the creamy white serum of extreme hypertriglyceremia. The patient was asymptomatic on admission. Ultracentrifugal lipoprotein studies were not done on his serum. Gofman and associates,[24] however, demonstrated that patients with (as they termed it) "essential hyperlipemia" do have a distinctive lipoprotein pattern with a marked elevation of the S_f 20-S_f 400 classes which contain large amounts of neutral fats. Lever, Herbst, and Lyons[18] also demonstrated these elevations and, in addition, found that two thirds of their patients with essential hyperlipemia had very large quantities of lipoproteins in the S_f 12-S_f 20 class.

Family history. Our patient's brother was said to have also had hyperlipemia, although it was not found in other members of the family. Lever and his group pointed out that it is impossible to really estimate the family incidence of this condition on the basis of the reports currently available. Many case reports contain no mention of the blood serum examination in relatives. In a review of 41 cases found in the literature, Lever, Smith and Hurley[3] found evidence of elevated serum lipids in one or more relatives involving seven cases.[3] Malmros, Swahn and Truedsson[25] studied two patients with essential hyperlipemia and found similar conditions in four members of one family and one member of the other. A familial incidence has been reported in other cases in adults.[6, 8]

Abdominal pain. Recurrent noncharacteristic abdominal pain has long been observed as a particularly striking feature of essential hyperlipemia. It has been noted in about one half of the reported cases. The pain varies in location and nature and has been described as aching and colicky. It has been described as being so severe as to suggest an acute abdominal emergency.[7] Sudden enlargement of the liver and spleen associated with an acute abdominal crisis was observed in one patient.[26]

Pancreatitis. The diagnosis of acute pancreatitis has been adequately established in at least nine reported cases by elevation of the amylase in the serum or urine, or by exploratory laparotomy.[3] It is probable that pancreatitis has been present in other cases which presented normal serum amylase values

since this finding is not incompatible with the diagnosis.[37] Hypertriglyceremia has been observed in acute pancreatitis presumably as a secondary phenomenon.[23] It has been pointed out that marked similarities exist between the syndrome of relapsing pancreatitis with hyperlipemia and essential familial hyperlipemia with abdominal pain. Pancreatitis and hyperlipemia has been described in siblings. Both patients with relapsing pancreatitis and essential hyperlipemia have been reported to have other family members with asymptomatic hyperlipemia. Xanthomatosis, which usually indicates hyperlipemia, has been noted to appear before the onset of abdominal pain in some cases of relapsing pancreatitis and in some cases of essential hyperlipemia. Hepatosplenomegaly has been frequently reported in both diseases and the blood lipid patterns are the same. It has also been observed that patients with frank chronic pancreatic insufficiency fail to develop hyperlipemia. Klatskin and Gordon[8] concluded from their studies that when chronic relapsing pancreatitis and hyperlipemia occur together, the pancreatitis is the result and not the cause of the hyperlipemia. This would *seem* to be true in our patient.

Lipemia retinalis. Lipemia retinalis is a rare condition sometimes seen in hyperlipemic states. The vessels of the fundi are pale yellow or salmon pink in color, and described as ribbon-like and flat. Because of the absence of an arteriolar light reflex, the differentiation of arterioles and veins must be made on size alone.[28] Joyner[7] found nine cases of essential hyperlipemia in which lipemia retinalis was reported. Holt[11] recently reported an additional case of lipemia retinalis in a child with essential hyperlipemia.

Hepatosplenomegaly. Hepatosplenomegaly has been reported in almost all childhood cases of idiopathic hyperlipemia up to 1953. This feature previously had been noted in about one half of the cases in adults.[7] A review of the more recent literature reveals organ enlargement of one or the other type in less than one third of the adult cases. A diet which is low in fat has resulted in a decrease in the size of the liver and spleen in a considerable number of patients.

Xanthomata. Lever, Smith, and Hurley[3] and Joyner[7] found descriptions of papular eruptive xanthomata in about one half of the reported cases of essential hyperlipemia. The lesions were described as yellow papules or nodules, most commonly located on the extensor surfaces of the knees, elbows, buttocks, thighs, and elsewhere. Many physicians have found that these lesions decrease or disappear on a low-fat diet. Lever, Smith, and Hurley[3] stated that "Apparently there is no critical level for either neutral fat or cholesterol at which the xanthomatous lesions appear." Both Lever[3] and Malmros[25] and their associates found xanthoma tuberosum associated with essential hyperlipemia. It is likely that these conditions represent the same

or similar metabolic defects inasmuch as the ultracentrifugal lipoprotein pattern also is similar, and patients with xanthoma tuberosum may have translucent serum. Gofman and his coworkers[24] found striking differences in the serum lipoprotein pattern between cases of essential hyperlipemia and "xanthoma tendinosum." Others,[3,15] however, have described xanthoma tendinosum in patients who ostensibly had essential hyperlipemia, and it would seem reasonable at this time to conclude that the presence of any particular xanthomatous lesion should not make, or preclude, the diagnosis of essential hyperlipemia.

Concomitant conditions. This diagnosis is ordinarily incompatible with the presence of nephrosis or diabetic acidosis. It is yet possible that essential hyperlipemia can exist concomitantly with other hyperlipemic states. Thannhauser[2] suggested that, in the rare situation where creamy white serum has been found in the presence of hypothyroidism, essential hyperlipemia is present. Hyperlipemia has been seen in severe untreated diabetes mellitus. This is completely reversible by adequate treatment of the diabetes, but does not respond to a low-fat diet.[14] Glycosuria and elevated blood sugars have been found in some patients with essential hyperlipemia.[10] Joske[15] and Adlersburg and Wang[14] reported cases of mild diabetes mellitus associated with idiopathic hyperlipemia. In these cases, insulin was only effective in reducing the blood lipids to the basic levels of idiopathic hyperlipemia, and the blood lipid levels remained above normal, even on low-fat diets. Lactescent serum occurs in a small proportion of patients with acute pancreatitis.[23] The relationship of relapsing pancreatitis and essential hyperlipemia has been mentioned and is discussed thoroughly elsewhere.[8] Adlersburg and Wang[14] suggested the possibility that diabetes mellitus and glycosuria in essential hyperlipemia frequently may be secondary to the relapsing pancreatitis found in this disease.

Prognosis and Treatment

The relationship of blood lipid abnormalities to atherosclerosis in essential hyperlipemia and other conditions is not fully understood. Increases in the blood cholesterol, the cholesterol to phospholipid ratio, the beta lipoproteins, and the "atherosclerogenic band" of the lipoproteins have been studied in this respect with inconclusive results.[17,19,29,30] It has been observed, however, that increases in the ultracentrifugal lipoprotein classes like those found in essential hyperlipemia may be associated with atherosclerosis.[18,19,29,30] About ten cases of essential hyperlipemia with adequate evidence of arteriosclerotic heart disease have been noted in the literature since 1954.[3,6,15,25,31] This number excludes those cases in which diabetes mellitus also was present. It is reasonable to conclude from these reports that essential hyperlipemia carries an un-

favorable prognosis in terms of premature cardiovascular disease. A low-fat diet may materially alter the abnormal blood lipid patterns and probably improve the prognosis. The strict adherence to low-fat diet therefore is the most important therapy available to patients with essential hyperlipemia. Wilkinson[32] advocated the spaced fat feeding method of treating these patients in which no more than one fatty meal in any 24-hour period is allowed.

Sitosterol has been used with moderate success in one case of essential hyperlipemia.[33] Intravenously administered heparin has been found to produce a marked decrease in the blood lipids and also produce a significant change toward the normal in the ultracentrifugal lipoprotein pattern.[31, 34] Chlorpromazine has been reported to have a similar effect.[34] Neither of these agents is recommended for general long-term use. Lecithin, choline, thyroxin, insulin, liver extract, pancreatic substance, and blood transfusions have been used in essential hyperlipemia with no noticeable effect.[26] The use of large doses of unsaturated fatty acids in the treatment of patients with this disease thus far has not been reported.

The Nature of Essential Hyperlipemia and Speculation

The exact nature of essential hyperlipemia remains obscure. Holt, Aylward, and Timbres[26] suggested that the hyperlipemia of this condition is due to the defective removal of the fat from the blood stream. Thannhauser[3] also classified this as retention hyperlipemia, similar to persistent alimentary hyperlipemia. Thannhauser and Stanley,[35] utilizing radioactive iodine technics, suggested that idiopathic hyperlipemia is caused by decreased utilization of the fat by the tissue. Holt,[11] using similar methods, was unable to support this contention. Alimentary hyperlipemia can be abolished by heparin, but at present there is inadequate evidence that the absence of a clearing factor similar to heparin in the blood is the cause of idiopathic hyperlipemia.[18] Wilkinson[32] hypothesized that the sluggish removal of fat from the blood, hepatosplenomegaly, and abdominal crises are a reflection of a genetic homozygous abnormality in essential hyperlipemia. He further assumed that fat gradually accumulates in the blood over a long period because the lipids never quite return to the fasting level before a new fat meal is ingested.

Dragstedt and associates[36] made some interesting observations in experimental animals on the relationship of the pancreas to hyperlipemia. They indicated that although insulin-treated, depancreatized dogs showed a profound fall in the serum lipids, dogs subjected to a *subtotal* pancreatectomy demonstrated a *hyperlipemia* and required considerably more insulin. In this second group of dogs, with only a small portion of functioning pancreatic tissue, deviation of the pancreatic juice from the intestine reversed the hyperlipemia and need for additional

insulin. Their work suggests that hyperlipemia may result from situations where adequate pancreatic juice allows fat absorption, but inadequate pancreatic internal or endocrine secretion prevents regulation of the serum lipids. It also was pointed out that alloxan-treated dogs, in which the beta cells are destroyed, develop an insulin-resistant diabetes although hyperlipemia is not present. Inasmuch as the alpha cells are intact in these animals, there has been some speculation on their ability to produce an internal secretion capable of controlling the blood lipids.[36] It has been reported that glucagon, the hyperglycemic factor produced by the alpha cells, reduces alimentary hyperlipemia[23] and that destruction of the alpha cells is followed by a gradual increase in the serum lipids.[37]

The site of the fundamental lesion in essential hyperlipemia is not known, but a substantial number of patients have demonstrated unequivocal evidence of pancreatitis. Acute pancreatitis is known to cause hypertriglyceremia, transient glycosuria, and even diabetes mellitus. The difficulty in establishing pancreatitis as an etiologic factor in essential hyperlipemia is that (1) excellent evidence is available that hypertriglyceremia has preceded overt evidence of pancreatic inflammation, (2) chronic pancreatitis with frank pancreatic insufficiency is rarely if ever associated with hyperlipemia, and (3) pancreatitis is not apparent in many cases of essential hyperlipemia. On the other hand, there is really little evidence to support the hypothesis that hypertriglyceremia can cause pancreatitis on the basis, for instance, of fat embolization. Perhaps essential hyperlipemia is actually an inherited inflammatory disease of the pancreas which primarily involves the "lipid regulating tissue" to cause asymptomatic hyperlipemia and secondary effects. If this were true, then the appearance of abdominal pain and clinical pancreatitis would merely indicate exacerbation of a subclinical process already responsible for hypertriglyceremia and explain a perplexing time relationship in the association of pancreatitis and essential hyperlipemia. This relationship remains an interesting problem in need of more thorough elucidation.

SUMMARY

Hypertriglyceremia, idiopathic and familial in nature, is called essential hyperlipemia. The fasting serum is usually milky white in this disease. About seventy cases have been reported, and another is presented. The classical features of this disease include: (1) opaque, white serum in the fasting state; (2) a family history; (3) recurrent abdominal pain; (4) lipemia retinalis; (5) hepatosplenomegaly; and (6) xanthoma of the skin. The case reported was observed for an 11-year period.

Recent reports indicate that essential hyperlipemia is associated with premature atherosclerosis and carries an unfavorable

prognosis. A low-fat diet is the best possible treatment for this disease and may improve the prognosis. The nature of essential hyperlipemia is not known but the disease seems to be related to pancreatitis in some way. This relationship is poorly understood, but there is some evidence that a lipid-regulating tissue of the pancreas is injured in essential hyperlipemia, allowing abnormally high blood fat levels in the presence of normal fat absorption.

REFERENCES

1. Burger, M., and Grütz, O.: Über hepatosplenomegale Lipoidose mit xanthomatösen Veränderungen im Haut und Schleimhaut. *Arch. f. Dermat. u. Syph.* 166: 542-575, Oct. 1932.

2. Thannhauser, S. J.; *Lipidoses: Diseases of the Cellular Lipid Metabolism.* Edited by Henry A. Christian. 2d edition. Oxford University Press, New York, N. Y., 1950.

3. Lever, W. F.; Smith, P. A. J.; and Hurley, N. A.: Idiopathic hyperlipemia and primary hypercholesteremic xanthomatosis; Clinical data and analysis of plasma lipids. *J. Invest. Dermat.* 22: 33-51, Jan. 1954.

4. Lever, W. F.; Smith, P. A. J.; and Hurley, N. A.: Idiopathic hyperlipemia and primary hypercholesteremic xanthomatosis; analysis of plasma proteins and lipids by means of electrophoresis and fractionation of plasma proteins; effect of high speed centrifugation and of extraction with ether on plasma proteins and lipids. *J. Invest. Dermat.* 22: 53-69, Jan. 1954.

5. Lever, W. F.; Smith, P. A. J.; and Hurley, N. A.: Idiopathic hyperlipemia and primary hypercholesteremic xanthomatosis; effects of intravenously administered heparin on plasma proteins and lipids. *J. Invest. Dermat.* 22: 71-87, Jan. 1954.

6. Martt, J. S., and Conner, W. E.: Idiopathic hyperlipemia associated with coronary atherosclerosis. *A. M. A. Arch. Int. Med.* 97: 492-496, Apr. 1956.

7. Joyner, C. R., Jr.; Essential hyperlipemia. *Ann. Int. Med.* 38: 759-777, Apr. 1953.

8. Klatskin, G., and Gordon, M.: Relationship between relapsing pancreatitis and essential hyperlipemia. *Am. J. Med.* 12: 3-23, Jan. 1952.

9. Corazza, L. J., and Myerson, R. M.: Essential hyperlipemia; report of 4 cases with special reference to abdominal crises. *Am. J. Med.* 22: 258-263, Feb. 1957.

10. Garunas, A.: Abdominal pain in essential hyperlipemia. *J. A. M. A.* 163: 1135-1137, Mar. 30, 1957.

11. Holt, K. S.: Idiopathic hyperlipaemia: report of case studied with radioactive iodine-labelled fat. *Arch. Dis. Childhood.* 32: 142-145, Apr. 1957.

12. Borrie, P. F.: Essential hyperlipaemia. *Brit. J. Dermat.* 69: 223, June 1957.

13. Millen, R. S.; Russ, E. M.; Eder, H. A.; and Barr, D. P.: Pregnancy complicated by hyperlipemia. *Am. J. Obst. & Gynec.* 71: 326-330, Feb. 1956.

14. Adlersberg, D., and Wang, C. I.: Syndrome of idiopathic hyperlipemia, mild diabetes mellitus, and severe vascular damage. *Diabetes* 4: 210-218, May-June 1955.

15. Joske, R. A.; Essential hyperlipaemia. *Med. J. Australia* 1: 826-831, June 4, 1955.

16. Harper, H. A.: *Review of Physiological Chemistry.* 6th edition. Lange Medical Publications, Los Altos, Calif., 1957.

17. Cantarow, A., and Trumper, M.: *Clinical Biochemistry.* 5th edition. W. B. Saunders Company, Philadelphia, Pa., 1955. pp. 80-123.

18. Lever, W. F.; Herbst, S. M.; and Lyons, M. E.: Idiopathic hyperlipemia and primary hypercholesteremic xanthomatosis; analysis of serum lipoproteins by means of ultracentrifuge before and after administration of heparin. *A. M. A. Arch. Derm.* 71: 158-170, Feb. 1955.

19. Gofman, J. W.; Glazier, F.; Tamplin, A.; Strisower, B.; and De Lalla, O.: Lipoproteins, coronary heart disease, and atherosclerosis. *Physiol. Rev.* 34: 589-607, July 1954.

20. Zilversmit, D. B.: Current concepts of lipide metabolism. *Am. J. Med.* 23: 120-133, July 1957.

21. Thannhauser, S. J.: Serum lipids and their value in diagnosis. (Medical Progress section). *New England J. Med.* 237: 515-522, Oct. 2, 1947; 546-552, Oct. 9, 1947.

22. Albrink, M. J.; Man, E. B.; and Peters, J. P.: Relation of neutral fat to lactescence of serum. *J. Clin. Invest.* 34: 147-157, Feb. 1955.

23. Albrink, M. J., and Klatskin, G.: Lactescence of serum following episodes of acute alcoholism and its probable relationship to acute pancreatitis. *Am. J. Med.* 23: 26-33, July 1957.

24. Gofman, J. W.; Rubin, L.; McGinley, J. P.; and Jones, H. B.: Hyperlipoproteinemia. *Am. J. Med.* 17: 514-520, Oct. 1954.

25. Malmros, H.; Swahn, B.; and Truedsson, E.: Essential hyperlipaemia. *Acta med. scandinav.* 149: 91-108, 1954.

26. Holt, L. E., Jr.; Aylward, F. X.; and Timbres, H. G.: Idiopathic familial lipemia. *Bull. Johns Hopkins Hosp.* 64: 279-314, May 1939.

27. O'Brien, J. J., and Thayer, T. R.: Pancreatitis; observations on 131 patients. *New England J. Med.* 253: 355-360, Sept. 1, 1955.

28. Franklin, E. C., and Weissman, M.: Serum lipids in lipemia retinalis; report of case. *Ann. Int. Med.* 46: 413-419, Feb. 1957.

29. Gofman, J. W.; Jones, H. B.; Lindgren, F. T.; Lyon, T. P.; Elliot, H. A.; and Strisower, B.: Blood lipids and human atherosclerosis. *Circulation* 2: 161-178, Aug. 1950.

30. Gofman, J. W.; Jones, H. B.; Lyon, T. P.; Lindgren, F. T.; Strisower, B.; Colman, D.; and Herring, V.: Atherosclerosis. Symposium; blood lipids and human atherosclerosis. *Circulation* 5: 119-134, Jan. 1952; correction 5: 797, May 1952.

31. Soffer, A., and Murray, M.: Prolonged observations of cardiovascular status in essential hyperlipemia; with special reference to serum lipid response to heparin. *Circulation* 10: 255-264, Aug. 1954.

32. Wilkinson, C. F., Jr.: Spaced fat feeding; régime of management for familial hyperlipemia. *Am. Int. Med.* 45: 674-680, Oct. 1956.

33. Best, M. M.; Duncan, C. H.; Van Loon, E. J.; and Wathen, J. D.: Effects of sitosterol on serum lipids. *Am. J. Med.* 19: 61-70, July 1955.

34. Hollister, L. E., and Kanter, S. L.: Essential hyperlipemia treated with heparin and chlorpromazine. *Gastroenterology* 29: 1069-1076, Dec. 1955.

35. Thannhauser, S. J., and Stanley, M. M.: Serum fat curves following administration of I^{131} labeled neutral fat to normal subjects and those with idiopathic hyperlipemia. *Tr. A. Am. Physicians* 62: 245-262, May 1949.

36. Dragstedt, L. R.; Clarke, J. S.; Hlavacek, G. R.; and Harper, P. V., Jr.: Relation of pancreas to regulation of blood lipids. *Am. J. Physiol.* 179: 439-450, Dec. 1954.

37. Caren, R., and Carbo, L.: Pancreatic alpha-cell function in relation to cholesterol metabolism. *J. Clin. Endocrinol. Metab.* 16: 507-516, Apr. 1956.

SURGEON WITHOUT HANDS

"The advent of anesthesia abolished the major need for excessive speed in operating and permitted a more deliberate and considered approach in contrast to the headlong, inflexible routine of the preanesthetic era. Anesthesia also made possible more complex operations which on this account alone were less likely to be performed repeatedly in a slavishly identical way. A further step in the evolution of surgery away from a rigidly stylized, mechanical craft was the application of basic science to everyday management of the surgical patient. Indeed, we have come a long way toward that millennium envisaged by Harvey Cushing when he looked to the day that university authorities would appoint as professor of surgery a man with no hands."

—C. ROLLINS HANLON, M. D.
in *Surgery, Gynecology & Obstetrics*
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HEARING LOSS FOLLOWING INADEQUATE TREATMENT OF OTITIS MEDIA

BYRON G. McKIBBEN, *Colonel, MC, USA*

THE use of therapeutic agents, developed during the past 20 years, has altered the clinical course of acute otitis media to such an extent that its more dangerous complications, such as acute mastoiditis, extradural and subdural abscess, lateral sinus thrombosis, suppurative meningitis, and abscess of the brain, have become much less frequent;[1] while a less dramatic, and frequently unrecognized, complication, that of hearing loss, has become more common.

Prior to the introduction of the sulfa drugs, the treatment of acute otitis media was primarily a surgical problem. In that era, myringotomy and evacuation of fluid from the middle ear was a common procedure. It was performed, not only by the otolaryngologist, but also by the general practitioner and by the pediatrician. With the relief of tension, the pain subsided, the infection was cured, and the hearing returned to normal. This procedure was performed early, in an effort to prevent bacterial invasion of the bony structures of the mastoid process and the petrous pyramid. The slogan of my pediatrics professor was "strip that child and look at his ears," and it was not uncommon to do a myringotomy during the course of a physical examination. Simple mastoidectomy was a common procedure and it was considered to be as much of an emergency as appendectomy. While serous otitis media, frequently referred to as secretory otitis media, has been well known since 1867, when it was first observed and described by Politzer,[2] it was not considered to be a serious problem; and some otolaryngologists apparently never recognized the condition until after the advent of chemotherapeutic and antibiotic drugs.

INFLUENCE OF THE SULFA DRUGS

With the introduction of sulfanilamide and its various derivatives, the management of middle-ear infections became a combined medical and surgical effort. Sulfa drugs were administered, but myringotomy was still considered essential in the presence of a middle-ear suppuration. With this combined medical and surgical management, the course of the disease was influenced favorably and its dangerous sequelae were less commonly ob-

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From William Beaumont Army Hospital, El Paso, Tex.

served. Chronic middle-ear effusion had not yet emerged as a serious threat to hearing acuity, because incision and drainage of localized pus was still recognized as a surgical principle that could not be disregarded.

INFLUENCE OF THE ANTIBIOTICS

Shortly after the termination of World War II, penicillin became available in large enough quantities to permit its use in many infectious processes. As the product was improved and its low toxicity became well known, it was evident that the dosage could be greatly increased. This factor of low toxicity gave penicillin a great advantage over the sulfa drugs, large doses of which were precluded because of increased toxicity. Since the advent of penicillin, many other antibiotics have been added to our armamentarium in the struggle against infectious diseases. The antibiotics have been so effective in the treatment of disease that it has been said that antibiotics have changed the face of medicine and that they have also changed the character of disease.[3]

Penicillin, when administered in adequate dosage early in the course of acute otitis media, generally causes a prompt subsidence of pain. Acetylsalicylic acid and, in some cases, codeine may be required to relieve pain during the first 24 hours. Penicillin, or one of the other antibiotics, usually is given for a period of three to five days—in many instances, this consists of a single intramuscular injection followed by a few days of penicillin by mouth. Because of the false impression that the patient is cured, together with possible unfamiliarity with the difference in appearance between a normal tympanic membrane and a nearly normal one, further observation and treatment usually are not considered necessary. This, of course, represents unsound clinical judgment and leads one into a false sense of security.

One must not lose sight of the masking effect of these drugs. The infectious process may lie dormant or actually progress to a surgical condition in the mastoid or to a serious intracranial complication. Most of these sequelae occur in patients who have had inadequate antibiotic therapy, have not had a myringotomy, and have not had adequate follow-up observation. These sequelae may not be accompanied by alarming symptoms and may be difficult to diagnose.

Morrow[4] deplored the practice of early abandonment of antibiotic treatment. He stated that it was known to be a frequent practice for acute otitis media to be treated by a single injection of penicillin with the matter of follow-up observation being left to the discretion of the patient.

Many of these patients will recover completely. An alarming number, however, if examined with an otoscope, will be found

to be in need of further treatment; and many of them will complain of impaired hearing in one or both ears. Otoscopic examination will reveal some abnormality in the appearance of the tympanic membrane. The type of abnormality will vary considerably, depending on the virulence of the infection, the sensitivity of the causative organism to the therapeutic agent, the dosage in which the drug is administered, and the natural immunity of the patient. The tympanic membrane may be light red or pink in color, the landmarks may be obliterated, and the luster may not have returned to normal; or it may be a dull gray with dilatation of the blood vessels on its surface, and the landmarks may just be returning. If the infection has been mild or the response to treatment was prompt, the drum may appear normal to the untrained eye; more careful observation, however, may reveal serous fluid in the middle ear. If considerable time has elapsed since the acute stage, any of the signs of serous otitis media may be observed. In this case the drum may present a salmon-pink or amber color, and a fluid level or bubbles may be seen in the middle ear. This observation, of course, makes the diagnosis easy. In the majority of cases, however, a fluid level or bubbles in the middle-ear effusion will not be seen because the middle ear is completely filled, or because of a thickened or opaque tympanic membrane.

Hoople[5] stated that ". . .a full tympanum, and, much more often than not the full mastoid as well, is ten times as prevalent as the ear which has only a (fluid) level line." He emphasized that the identifying feature is the over-all amber color of the drum, which may vary from a faint, barely perceptible yellowish tinge to a dark, bluish cast, and that in the majority of these cases a helpful aid in making a diagnosis is the fact that the short process and handle of the malleus stand out as chalky white in contrast to the colored drum.

Walsh[6] stated that a creamy-dull appearance to the drum is suggestive of a glue-like mucoid exudate in the middle ear. Day[7] first applied the term "glue ear" to this condition some 25 years ago when it was called to his attention by his father. To become familiar with the appearance of the tympanic membrane in these cases, an otoscopic examination should be performed on all patients undergoing physical examination.

Davison,[8] Walsh,[6] and Day[9] stressed the importance of the information to be gained by use of the pneumatic otoscope (figs. 1 and 2). If there is fluid in the middle ear, the tympanic membrane moves poorly and the degree of immobility is in proportion to the amount of fluid in the middle ear. If the drum moves rapidly in response to rapid alteration in air pressure produced by the hand bulb, there is little or no fluid in the middle ear. Walsh stated that an otologic examination that does not include use of the pneumatic otoscope is incomplete.

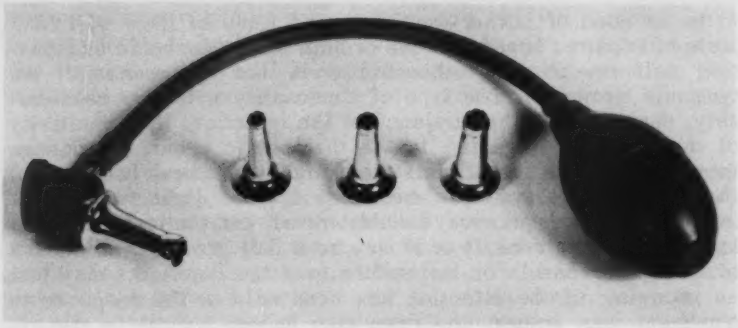

Figure 1. The Bruening pneumatic otoscope, shown above, is much more satisfactory than the standard Siegel's otoscope. The contour of the specula, which come in six sizes (size 0 and 00 not shown above) allows an air-tight fit in nearly all ears, without undue discomfort. This instrument must be used with a head mirror and a good source of light.

A striking example of mismanagement, resulting from unfamiliarity with one of the typical appearances of the tympanic membrane when fluid is in the middle ear, was recently observed by Sheehy.[10] He performed bilateral myringotomies on a man who had been wearing a hearing aid for two and one-half years. Following the evacuation of serous fluid from both middle ears, the hearing returned to normal in one ear and was improved in the other (figs. 3 and 4). Needless to say, the man could hardly believe that the hearing aid could be discarded. He had previously been examined by at least three physicians who were considered to be capable of performing an otoscopic examination, but they failed to recognize the true nature of his hearing loss and gave him a diagnosis of otosclerosis.

An even more dramatic example of failure to recognize a case of hearing loss resulting from middle-ear effusion was observed by Day.[9] He performed bilateral myringotomies on a child who for six years had been in a school for the deaf. After the myringotomies had been performed, the middle ears appeared to be free of exudate. Thick, stringy, mucoid material, however, was removed by careful application of spot suction; and the child's hearing was restored to normal. He emphasized that in these cases of "glue ear" the tympanic membrane is immobile when examined with the pneumatic otoscope; and, that in order to effect a cure, the glue-like mucoid exudate must be removed by spot suction after performing a myringotomy under general anesthesia.

The experimental studies of Wehrs and Proud[11] further emphasized the fact that middle-ear effusion may be difficult to recognize and that a diagnostic myringotomy is justified in all cases of conductive hearing loss where the examiner is unable

Figure 2. The electric otoscope with battery handle may be converted into a pneumatic otoscope with the rubber bulb attachment as shown above. This instrument is convenient for house calls or for the physician who does not use the head mirror. An air-tight fit, however, will be impossible in some ears where the Bruening otoscope (fig. 1) will be found to be satisfactory.

to determine that the middle ear is free of fluid. They performed bilateral myringotomies on 72 children with conductive hearing loss, regardless of the condition of the tympanic membrane, and removed fluid by spot suction in each one. Apparently some of these drums appeared normal. Wehrs and Proud failed to mention the pneumatic otoscope, and it is assumed that they did not use it. As previously mentioned, this instrument is a definite diagnostic aid and should be used in all of these cases.[6, 8]

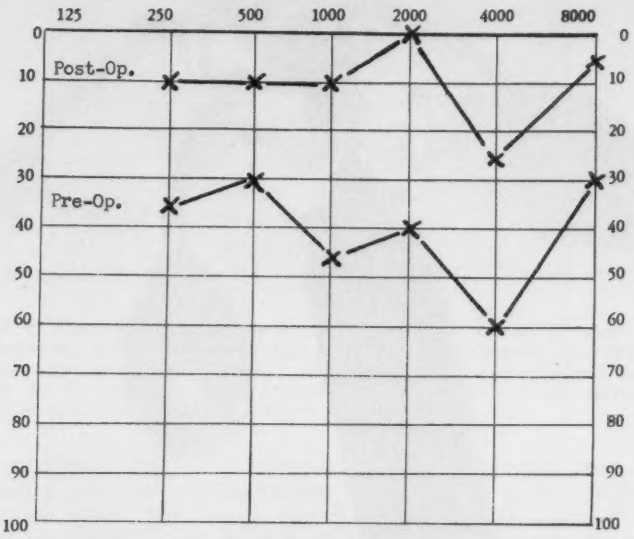

Figure 3. Left ear. Pre-Op.: There was 38-decibel loss in the speech frequencies (500-1,000 and 2,000 cycles per second) prior to myringotomy. Post-Op.: Normal hearing after myringotomy and evacuation of serous fluid. The 25-decibel loss at 4,000 cycles per second is typical of early hearing loss in persons who are exposed to noise—gunfire in this case.

The impression that acute otitis media is no longer a disease that requires surgical intervention has been widespread during the last 15 years. In 1953 Rutherford[12] stated that the complacent acceptance of the antibiotics as a cure-all in middle-ear infections had resulted in a state where the younger pediatricians were unfamiliar with the technic of cleansing the ear canal, that they were unable to observe and recognize the changes in the drum membrane which indicate pathologic processes in the middle ear, and that they did not know how to perform a myringotomy. She further emphasized that some interns and residents were taught that myringotomy was a procedure to be avoided because it injured the tympanic membrane, although spontaneous rupture under antibiotic therapy apparently was not considered to be harmful. She advocated the use of antibiotics in the treatment of acute otitis media, only after myringotomy and general therapeutic measures have failed to effect a cure.

DeWeese[13] commented that pediatric teaching was almost unanimous in emphasizing that myringotomy was unnecessary. He stated that it was unfortunate that students, interns, resi-

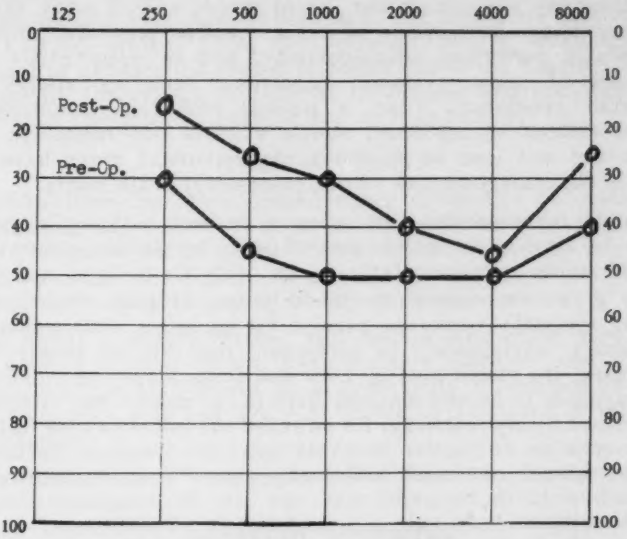

Figure 4. Right ear. Pre-Op.: There was 48-decibel loss in the speech frequencies prior to myringotomy. Post-Op.: After myringotomy, the hearing was improved to the 31-decibel level—borderline between good and bad hearing. A small perforation in the posterior portion of Schrapnell's membrane (pars flaccida), discharging foul-smelling exudate, indicates chronic infection of the epitympanic space and mastoid, and probably a cholesteatoma. This accounts for failure of the hearing to return to normal after myringotomy and evacuation of serous fluid. Modified radical mastoidectomy has been recommended for this ear.

dents, and, even more unfortunate, that parents and other lay people had been told repeatedly that myringotomy is injurious to the drum membrane.

The pediatrician[14] who discussed Rutherford's paper stated that if upper respiratory infections were properly treated, otitis media should be uncommon and that mastoiditis, chronic otorrhea, and deafness should be rare. He further stated that most of the cases of otitis media and its sequelae he had observed in one hospital occurred in the children who had had inadequate antibiotic therapy.

Rutherford stated that repeated attacks of acute secretory otitis media probably were the most common cause of chronic hearing loss and that in many instances these patients were being treated with antibiotics instead of measures to relieve the underlying cause, that of obstruction of the eustachian tube.

These cases require systemic decongestants such as ephedrine or Propadrine Hydrochloride (brand of phenylpropanolamine hydrochloride) vasoconstrictor nasal drops, and in many cases a myringotomy. Restoration of tubal function may also require a carefully performed adenoidectomy, and in some cases the treatment of some systemic condition, such as allergy or endocrine imbalance. When a patient with this condition is treated without myringotomy, sterile exudate may remain in the middle ear and lead to deafness. Antimicrobial drugs have no place in the management of serous (secretory) otitis media.

Dixon[15] recommended that when a patient with acute otitis media is first seen he be treated with crystalline penicillin, 500,000 units intramuscularly twice daily for 5 days, and that he be given vasoconstrictor nasal drops. If pain, fever, or a bulging tympanic membrane persist for 24 hours after treatment is started, myringotomy is performed; but this is usually unnecessary. He stated that if, after the acute stage has subsided, there appears to be any residual fluid in the middle ear, it should be removed by myringotomy. He stressed the necessity for follow-up observation at regular intervals until the tympanic membrane appears normal and until audiometry shows that the hearing is restored.

ANTIBIOTIC DEAFNESS

In 1949, Popper[16] first drew attention to a type of hearing loss which he termed "antibiotic deafness;" and again in 1957 he[3] described the condition, stating that a more explanatory title would be "antibiotic effusion deafness" in order to distinguish it from deafness caused by streptomycin sulfate.

Popper stated that this type of deafness is the result of the great potency and large dosage of antibiotics and that the efficiency of these curative agents has become a menace to the function of hearing.

He observed 93 cases of antibiotic deafness over a five-year period and stated that the diagnosis presented no difficulty. A typical history is that the patient had acute otitis media which responded promptly to antibiotic therapy; the pain was relieved without aural discharge; but hearing loss, noted either by the patient, or in the case of a child, by the mother, had not subsided. Otoscopic examination revealed that the tympanic membrane was not normal, and myringotomy with evacuation of fluid from the middle ear was followed by return of hearing to normal. Repeat myringotomy was necessary in 25 of his cases, and simple mastoidectomy was required in 18.

An interesting case was that of a farmer who was treated for severe earache with penicillin. The pain subsided within 24 hours without aural discharge, but severe deafness persisted.

While on a hunting trip where no medical facilities were available, earache recurred. The tympanic membrane ruptured spontaneously with copious discharge and immediate improvement in hearing acuity. This man refused further treatment with penicillin because he feared it would cause the hearing loss to recur. He therefore was referred to Popper who convinced him that with adequate drainage he had nothing to fear.[3]

PRESENT TREND

While there has been considerable difference of opinion as to when in the course of acute otitis media to start antibiotics and whether or not to perform a myringotomy, there is a growing tendency for physicians to agree on the importance of myringotomy in the management of this infectious process.

In 1953, DeWeese[13] stated that he believed there were signs of such a change in the pediatrician's attitude; and Bigler[14] intimated that this would be a possibility if antibiotics could not keep pace with new types of bacterial infections or organism resistance.

In 1955, Silcox[17] commented that we have reached an era where infections of the ear and adjacent structures are not being controlled by antibiotics and that the complications of acute otitis media are being seen more frequently because of the development of antibiotic-resistant strains of bacteria. He reported three cases of acute otitis media with rapid development of serious intracranial complications that were not controlled by antimicrobial drugs.

In 1956, Goodale[18] stated that the pendulum had begun to swing back toward the prechemotherapeutic era. He philosophized that we should have anticipated this as a typical biologic response; that in time, all life makes an adjustment to its changing environment or becomes extinct. He called attention to the increasing tendency for micro-organisms to develop resistance to antibiotics and mentioned the greater number of antibiotic-resistant organisms, such as *Proteus vulgaris* and *Pseudomonas aeruginosa,* that are being cultured from discharge from the middle ear. He further pointed out that patients frequently show allergic reactions to antibiotics and, therefore, are unable to be treated with them, even though the micro-organisms responsible for their infection may be sensitive to the drug.

This increasing resistance of micro-organisms to antibiotics induced Davison[8] to employ massive doses of penicillin. He performed early myringotomy and evacuated the exudate with spot suction. This fluid, collected under sterile precautions, provides an excellent sample for culture and sensitivity studies.

Cap[19] stressed the importance of early myringotomy in cases of acute otitis media with a bulging tympanic membrane and

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earache. He stated that in the Pediatrics Department, William Beaumont Army Hospital, antibiotics (usually procaine penicillin, 300 mg (300,000 units) daily; and Terramycin (brand of oxytetracycline), 50 mg per kilogram of body weight up to 1 gram daily) are routinely prescribed for a period of 10 days. Follow-up observation is continued until the tympanic membrane appears normal.

SUMMARY AND CONCLUSIONS

The use of antimicrobial drugs in the treatment of acute otitis media has resulted in a marked decrease in the intracranial suppurative processes that may complicate middle-ear infections. Coincident with this therapeutic achievement, and because of the widespread impression that myringotomy and evacuation of middle-ear fluid are no longer necessary, there has been an alarming increase in the incidence of hearing loss resulting from retained serous or mucoid, and even glue-like, exudate in the middle ear.

The emergence of strains of micro-organisms, showing an increasing resistance to antimicrobial drugs and resulting in an increasing incidence of failure to control acute otitis media and its complications, has induced many physicians to give larger doses of antibiotics and has made them more aware of the importance of myringotomy. Despite this favorable trend in the management of acute otitis media, far too many patients suffering from this condition are receiving inadequate antibiotic therapy and are being denied the benefit of myringotomy for the release of purulent exudate and for the alleviation of pain.

Before we can hope to see a decrease in the number of patients suffering from this type of hearing loss, all physicians who treat acute otitis media must appreciate that a bulging drum accompanied by pain is sufficient indication for myringotomy and evacuation of middle-ear exudate, that an effective antibiotic should be administered in adequate dosage, and that treatment should be continued until the drum appears normal and audiometric testing shows the hearing to be restored. These physicians must be familiar with the appearance of a normal tympanic membrane, and they must be able to recognize the changes that indicate myringitis, nonsuppurative otitis media, and suppurative otitis media. The findings in each case must guide them in their decision as to the treatment that is to be prescribed.

REFERENCES

1. Courville, C. B.: Symposium: intracranial complications of otitis media and mastoiditis in antibiotic era; modification of pathology of otitic intracranial lesions by antibiotic preparations. *Laryngoscope* 65: 31-46, Feb. 1955.

2. Politzer, A.: *A Textbook of the Diseases of the Ear and Adjacent Organs.* Translated and edited by James Patterson Cassels. Henry C. Lea's Son and Co., Philadelphia, Pa., 1883. pp. 260-302.

3. Popper, O.: Antibiotic deafness. *South African M. J.* 31: 54-56, Jan. 19, 1957.

4. Morrow, R. C.: Complications of mastoiditis in antibiotic era. *Ann. Otol. Rhin. & Laryng.* 67: 41-60, Mar. 1958.

5. Hoople, G. D.: Otitis media with effusion: A challenge to otolaryngologists. *Tr. Am. Acad. Ophth.* 54: 531-541, May-June, 1950; also in *Laryngoscope* 60: 315-329, Apr. 1950.

6. Walsh, T. E.: Discussion. In Davison, F. W.: Middle ear effusion—systemic factors. *Tr. Am. Laryng., Rhin. & Otol. Soc.*, 61st Annual Meeting, 21-23 May 1958. (To be published.)

7. Day, K. M.: Personal communication.

8. Davison, F. W.: Otitis media—then and now. *Laryngoscope* 65: 142-151, Mar. 1955.

9. Day, K. M.: Discussion. In Davison, F. W.: Middle ear effusion—systemic factors. *Tr. Am. Laryng., Rhin. & Otol. Soc.*, 61st Annual Meeting, 21-23 May 1958. (To be published.)

10. Sheehy, J. L.: Personal communication.

11. Wehrs, R. E., and Proud, G. O.: Conductive deafness in children. *A. M. A. Arch. Otolaryng.* 67: 16-19, Jan. 1958.

12. Rutherford, M. H.: Proper use of antimicrobial drugs in acute otitis media. *Tr. Am. Acad. Ophth.* 57: 53-62, Jan.-Feb. 1953.

13. DeWeese, D. D.: Discussion. In reference 12.

14. Bigler, J. A.: Discussion. In reference 12.

15. Dixon, J. W.: Acute otitis media in children treated without myringotomy; follow-up with audiometry in 88 cases. *J. Laryng. & Otol.* 72: 227-237, Mar. 1958.

16. Popper, O.: Discussion following Sir Alexander Fleming's opening address on antibiotics and Sir Lionel Whiby's on sulfa drugs, at *4th International Congress of Otolaryngology* in London, 1949. Quoted in reference 3.

17. Silcox, L. E.: Otitic complications with antibiotic resistant bacteria. *Laryngoscope* 65: 170-177, Mar. 1955.

18. Goodale, R. L.: Otology—acute middle-ear disease. (Medical Progress section) *New England J. Med.* 254: 118-122, Jan. 19, 1956.

19. Cap, T. W.: Personal communication.

THE HAZARDS OF RADIATION

"The hazards of radiation came dramatically into the news about 30 years ago, when a number of women employed to paint luminous dials on watches were stricken with radium poisoning. The extraordinary developments of the atomic energy industry in recent years, and the prospect of vast future growth, pose many medical and public health problems. While it appears that the activities at the major Atomic Energy Commission installations have had a good safety record, the growing use of radioactive isotopes in industrial plants, laboratories, hospitals, and other places is increasing the number of people exposed to radiation hazard. Maximum protection needs to be given persons working with atomic substances and equipment. The permissible levels for radiation exposure set by government agencies can serve as a guide for the maintenance of safety among workers in this field."

—in *Statistical Bulletin*
p. 7, Feb. 1958

RHEUMATIC FEVER IN MILITARY PERSONNEL

LEO E. HOLLISTER, *M. D.*
EPHRAIM P. ENGLEMAN, *M. D.*

RHEUMATIC FEVER is a military problem of some magnitude. During World War II approximately 40,000 cases of the disease occurred in the combined Armed Forces.[1] The disease ranked high as a noncombat cause of disability and loss of manpower. With prospects for a continuing large personnel in the Armed Forces, rheumatic fever will remain an important concern.

This report is based on a review of the records of 563 cases of rheumatic fever which occurred in military personnel during World War II. Four hundred and one patients with rheumatic fever were observed personally by one of us (E. P. E.) during World War II at an Army Rheumatic Fever Center (Torney General Hospital, Palm Springs, Calif.). Thirty-three of these patients, and 102 additional patients who had rheumatic fever in World War II, were observed in a follow-up study approximately six years after the attack of rheumatic fever in military service.[2] Medical records were reviewed on 60 additional veterans in connection with the follow-up study, although these veterans were not examined in person.

At the time of this study, modified Jones criteria were used for diagnosis.[3] As evidence of an attack of rheumatic fever the patient must have had at least one major manifestation (carditis, self-limited arthritis, subcutaneous rheumatic nodules, or chorea) and at least two minor manifestations (fever; arthralgia; abnormal laboratory tests; epistaxis or purpura; erythemas, including erythema marginatum; pneumonitis). Especially careful differential diagnosis was made to eliminate patients with rheumatoid arthritis, collagen disease, drug reactions, and other diseases which might mimic rheumatic fever.

BACKGROUND DATA

The 401 patients admitted to Torney General Hospital, a special rheumatic fever center, were in all stages of their disease at the time of admission. Most patients were in a subacute

From Veterans Administration Hospital, Palo Alto, Calif. and Veterans Administration Hospital, San Francisco, Calif.

or convalescent stage of rheumatic fever, having been initially treated at nearby station or general hospitals. Rather complete medical records were available on these patients, though the type of clinical and laboratory studies, as well as treatment, varied somewhat during the period prior to their admission to the rheumatic fever center. The 162 patients not admitted to Torney General Hospital were treated at nonspecialized general hospitals. No significant clinical differences were noted between this group and the Torney group in regard to clinical manifestations of illness or outcome. Consequently, it was believed that the group of patients studied was as nearly representative as any sample might be of patients with rheumatic fever in military service.

Approximately one half of the patients had their attack of rheumatic fever between the ages of 18 and 21 years. In 8 per cent, rheumatic fever occurred in patients 34 years of age or older. Ninety-four per cent of these patients were men, reflecting the preponderance of men in the military service. Of the 563 patients, only 201 had a history indicative of an attack of rheumatic fever prior to military service, a prevalence of 35.7 per cent. History of "rheumatic fever," "inflammatory rheumatism," "Saint Vitus' dance," or a "heart murmur" following a febrile illness were considered evidence of a previous attack. Two thirds of all patients had histories of tonsillitis or scarlet fever, suggesting previous streptococcal infection (table 1).

CLINICAL FINDINGS

Antecedent Illness. The clinical onset of rheumatic fever was preceded by a closely antecedent illness in 478 (85 per cent) of the 563 patients. In 443 of these patients, the illness was described as a "cold," "acute nasopharyngitis," "acute tonsillitis," or "acute sinusitis." Twenty-nine patients had scarlet fever, 3 had rubella, and 3 had an attack of diarrhea. In 10 other patients, episodes of unusual physical stress, such as prolonged hikes or immersions, preceded the appearance of rheumatic fever. Seventy-five patients had no recognized incident prior to the attack of rheumatic fever.

The majority of patients in whom an antecedent infection occurred had a latent and relatively asymptomatic period of seven to twenty-one days before the onset of acute rheumatic fever. When episodes of physical stress antedated the illness, symptoms of rheumatic fever occurred immediately thereafter.

Arthralgia and Arthritis. Arthralgia was present in 555 (98.8 per cent) of our 563 patients. Arthritis (objective changes in the joints) was present in 477 (85.3 per cent). The arthropathy involved many joints and was migratory in the majority of patients. It was usually the earliest clinical indication of rheumatic activity. Occasionally, patients complained of vague

pains in their joints for days or weeks before the acute manifestations appeared. The latter, however, usually marked the onset of the disease with initial involvement of one of the weight-bearing joints, most commonly the knee or ankle. In 81 per cent of the patients, the arthropathy was symmetrical and in approximately 50 per cent fingers and toes were involved. In 5 per cent of the patients only two joints were affected. Objective signs of joint disease were lacking in 14 per cent of the group. This factor helped to explain such early misdiagnoses as "sprain" and "flat feet."

TABLE 1. *Clinical findings in 563 patients with rheumatic fever**

History and clinical signs	Number of patients	Per cent
History		
Rheumatic fever	201	35.7
Tonsillitis or scarlet fever	376	66.6
Antecedent illness	478	85.3
Clinical signs		
Arthralgia	555	98.8
Arthritis	477	85.3
Carditis	231	41.0
Heart involvement at end of attack	114	20.3
Fever (over 99°F orally)	518	92.0
Elevated sedimentation rate	552	98.2
Good articular response to salicylate	450	80.0
Hemorrhagic manifestations	104	18.4
Erythemas	29	5.2
Pneumonitis	28	4.9
Subcutaneous rheumatic nodules	8	1.4
Chorea	2	0.4

*Average age of adult onset, 22 years; range from 18 to 42 years.

Following the institution of maximum tolerated doses of salicylates, objective manifestations in the joints usually disappeared in less than 7 days. They never lasted longer than 3 to 4 weeks. Permanent objective changes in the joints as the result of rheumatic fever were not observed, although some patients complained of prolonged arthralgia for many months after all signs of active disease had disappeared.

Carditis. Evidence of carditis was found in 231 of the 563 cases, an incidence of 41 per cent. The signs of carditis in these patients are listed in detail in table 2.

Auscultatory signs of carditis were more frequent than electrocardiographic signs. The outstanding auscultatory sign was the systolic murmur. Systolic murmurs were graded for intensity (1 to 4), and were evaluated according to location, duration, transmission, and quality. Grade 1 and Grade 2 systolic murmurs were considered to be of physiologic origin. Such murmurs, usually transient, were heard in 119 patients (21 per cent).

Various degrees of AV block and abnormalities of the ST segments and T waves were the most frequent electrocardiographic signs of carditis. Cardiac enlargement, pericarditis, and congestive heart failure were infrequent manifestations of carditis.

TABLE 2. *Manifestations of carditis in 231 of 563 military patients with rheumatic fever*

Manifestations of carditis	Number of patients	Per cent
Auscultatory	184	32.6
Systolic murmur, Grade 3 or more	131	23.3
Diastolic murmur, aortic	29	5.1
Systolic and diastolic murmur, mitral	16	2.8
Pericardial friction rub	21	3.7
Electrocardiographic	170	30.2
AV block (1st degree)	122	21.7
AV block (2nd degree)	13	2.3
AV block (3rd degree)	11	2.0
Abnormal ST & T waves	71	12.6
Bundle-branch block	1	0.2
Prolonged QT interval	4	0.8
Wandering pacemaker	10	1.8
Nodal rhythm	6	1.0
Paroxysmal tachycardia	3	0.5
False bundle-branch block	1	0.2
Other radiologic and clinical	9	1.5
Cardiac enlargement	9	1.5
Congestive heart failure	5	1.0

Residual signs of heart disease at the termination of an attack of rheumatic fever during military service were noted in 114 of the 563 patients in this series, an incidence of 20.3 per cent. Residual heart disease was determined by the presence of: (1) cardiac enlargement, (2) diastolic heart murmurs, (3) electrocardiographic abnormalities, (4) systolic heart murmurs of Grade 3 or more even in the absence of cardiac enlargement. In 100 patients (17.7 per cent) the residual abnormality was manifested by significant heart murmurs. In 22 patients (3.9 per cent), electrocardiographic abnormalities remained. In 8 patients (1.4 per cent), cardiac enlargement was present at the end of the attack.

Fever. Fever was observed in 518 (92 per cent) of these patients. The median range of temperature elevation was 101°F to 102°F but in more than one fourth of the group the maximum oral temperature did not exceed 100°F. The temperature usually returned promptly to normal with recovery from a rheumatic cycle.

Laboratory Tests. The sedimentation rate was elevated at or shortly after the onset of the disease in over 98 per cent of the patients, and it was usually the last laboratory sign to return to normal. The average duration of elevation of sedimentation

rate was 11 weeks, but in one third of the patients the elevation persisted beyond that time. Leukocytosis and anemia did not occur frequently enough to be considered as reliable signs of activity of the disease in themselves. Forty-nine per cent of the patients had an elevation of the antistreptolysin titer to more than 333 Todd units but this test was not performed in every patient and not always early in the disease. Undoubtedly the frequency of elevated antistreptolysin titers would have been greater had this test been obtained constantly.

Response to Salicylates. The articular response to salicylates given in maximum tolerated dose was excellent in 80 per cent of these patients. In general, objective changes in the joints disappeared within seven days after starting therapy. Frequently, a recrudescence of arthritis occurred if salicylates were withdrawn prematurely. The effect of salicylates on the cardiac manifestations of rheumatic fever was not appreciable. A prompt and effective articular response to salicylates almost always constituted a fairly reliable diagnostic criterion for rheumatic fever. All these patients were treated prior to the clinical use of adrenocortical hormones in rheumatic fever.

Additional Clinical Manifestations. Epistaxis, purpura, or petechiae were seen in 104 (18.4 per cent) of the 563 patients. Skin eruptions occurred in 29 (5 per cent); erythema marginatum was observed in 10 patients; urticaria was found in 12 patients, and erythema nodosum in the remaining 7. Pneumonitis occurred in 28 patients. It was virtually impossible to differentiate rheumatic pneumonitis from so-called primary atypical pneumonia, which may have been the diagnosis in some cases. Subcutaneous rheumatic nodules were observed in only 8 patients. Chorea was also rare, occurring in only 2 of the patients. Both of these patients had a history of rheumatic fever in childhood.

DISCUSSION

The epidemiologic factors of most importance in these patients were the presence of an antecedent infection and a past history of rheumatic fever. Antecedent infections were recorded in 85 per cent of our cases, which is similar to the incidence of 75 per cent more recently recorded.[4] While the presence of an antecedent infection is no guarantee of rheumatic fever, its absence should demand strong additional support for the diagnosis. The prevalence of a past history of rheumatic fever varies greatly in adults with the disease, ranging from 5 to 54 per cent. However, it appears that more than one quarter of all patients have previously had rheumatic fever. The presence of such a history increases the likelihood of a rheumatic recurrence, while its absence does not mitigate against the diagnosis.

Evidence of carditis and a self-limiting polyarthritis responding well to salicylates were the most important clinical signs of rheumatic fever. Subcutaneous nodules, chorea, and erythema marginatum were rare manifestations of the disease at this age, and in none of our cases occurred without arthritis or carditis. In adults, arthritis is much more frequent than carditis, at least twice as often in these patients. More than three-quarters of patients with significant carditis were diagnosable by auscultatory signs. However, in a number of patients, electrocardiographic abnormalities were the sole evidence of carditis. Only 7 of the 563 patients were diagnosed as having rheumatic fever in the absence of signs or symptoms of joint disease. In 9 other patients, the signs of carditis preceded those of arthritis, in one instance by as much as 4 months. Several studies have disclosed that carditis without, or preceding, arthritis may occur in adults with rheumatic fever.[5, 6]

A frequent problem in the diagnosis of carditis is the proper evaluation of systolic murmurs, usually apical, which are not easily heard. When such murmurs occur without other evidence of heart disease, even during the acute stage of rheumatic fever, it is doubtful that they should be considered as indicative of carditis. A follow-up study of veterans with rheumatic fever in World War II provided a particularly good retrospective analysis of such murmurs.[3] Although such systolic murmurs were heard in 46 of 135 patients during the adult rheumatic attack, only one had a murmur considered significant when observed 4 to 8 years later. Twenty-five still had a Grade 1 systolic murmur, while 20 no longer had audible murmurs. This experience leads us to conclude that heart murmurs which would be considered physiologic probably are, even in the presence of acute rheumatic fever.

Residual heart disease was found in 20.3 per cent of the patients in this study, a prevalence comparable to that observed by others.[7-9] This low prevalence of cardiac affection is below that reported for children. It should be remembered that it does not reflect any effect from treatment with corticosteroids. Considerable prognostic significance can be attached to the fact that the heart usually remains unchanged for several years after an attack of rheumatic fever in adult life.

Since World War II, the diagnostic criteria for rheumatic fever have been changed.[10] Major manifestations now include carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum. Minor criteria include fever, arthralgia, atrioventricular block, abnormal laboratory tests (increased ESR, WBC, or presence of C-reactive protein), preceding beta-hemolytic streptococcal infection, or previous history of rheumatic fever. A diagnosis of rheumatic fever requires the presence of at least two major criteria or the combination of one major and two minor criteria. Even with the revised criteria, the cases in this study

would still have been diagnosed as rheumatic fever. However, a considerable number would have been so diagnosed on the basis of the weakest combination possible (polyarthritis, fever, and elevated ESR). The relative rarity in military personnel of three major criteria (chorea, subcutaneous nodules, and erythema marginatum) and the difficulty in definitely proving preceding streptococcal infection (unavailability or oversight in obtaining throat cultures or antistreptolysin titers) reduces the number of usable diagnostic criteria. In such cases, a presumptive antecedent streptococcal infection or a past history of rheumatic fever may add to the security of the diagnosis.

The long period during which military patients are customarily observed during such an illness tends to eliminate other confounding diseases such as collagen diseases, bacterial endocarditis, leukemia, sickle cell anemia, tuberculosis, poliomyelitis, and infectious mononucleosis. Most difficulty in diagnosis arises in distinguishing between rheumatoid arthritis and rheumatic fever. The presence of an antecedent infection or a self-limiting course with a good response to salicylates favors rheumatic fever but is not entirely reliable. The new serologic tests for rheumatoid factor are not likely to be helpful in the differential diagnosis early in the course. Persistent arthralgia, even after all other clinical evidences of rheumatic activity have subsided, may add to the confusion. Post-rheumatic arthralgia lasting as long as six years following a rheumatic attack in military service was found in two-thirds of the patients seen in our follow-up study.[2] In no case were objective changes found in the affected joints to support a diagnosis of rheumatoid arthritis.

SUMMARY

The clinical aspects of rheumatic fever in military personnel were reviewed in 563 cases occurring during World War II.

A previous history of rheumatic fever was discovered in slightly more than one third of the patients. Previous histories suggesting streptococcal infection were found in two thirds of patients. A closely antecedent illness occurred in 85 per cent of cases. Younger adults, usually below the age of 21 years, were most frequently affected.

Polyarthritis, which occurred in 85 per cent of patients, was the most important clinical manifestation. Characteristically, it was self-limiting, responding to salicylate therapy. Carditis, manifested in most cases by the presence of pathologic heart murmurs, was found in only 41 per cent of patients. In some patients, the only manifestations of cardiac involvement were electrocardiographic abnormalities, mainly atrioventricular block and ST-T abnormalities. Other common clinical findings were fever, arthralgia and elevated sedimentation rate. Erythema

marginatum, subcutaneous nodules and chorea were rare in these patients. For this reason, a previous history of rheumatic fever, a well-documented antecedent streptococcal infection, or atrioventricular block may be more reliable diagnostic criteria in adult patients.

Residual heart disease following rheumatic fever was present in 20 per cent of these patients. Such heart disease was manifested by a pathologic heart murmur in most cases. This favorable outcome was obtained prior to the use of corticosteroids.

REFERENCES

1. Beebe, G. W.: Division of Medical Sciences, National Research Council. Personal communication.

2. Engleman, E. P.; Hollister, L. E.; and Kolb, F. O.: Sequelae of rheumatic fever in men; four to eight-year follow-up study. *J. A. M. A.* 155: 1134-1140, July 24, 1954.

3. Jones, T. D.: Diagnosis of rheumatic fever. *J. A. M. A.* 126: 481-484, Oct. 21, 1944.

4. Carmichael, D. B.: Continuing military problem of rheumatic fever. *U. S. Armed Forces M. J.* 7: 399-406, Mar. 1956.

5. Cohn, A. E., and Lingg, C.: Natural history of rheumatic cardiac disease: Statistical study. *J. A. M. A.* 121: Jan. 2, 1943.

6. Rantz, L. A.; Spink, W. W.; and Boisvert, P. J.: Abnormalities in electrocardiogram following hemolytic streptococcus sore throat. *Arch. Int. Med.* 77: 66-79, Jan. 1946.

7. Manchester, R. C.: Rheumatic fever in naval enlisted personnel; analysis of major manifestations observed, factors involved in its occurrence and cardiac residue. *Arch. Int. Med.* 77: 317-331, Mar. 1946.

8. Kimbro, R. W.: Report of 100 cases of rheumatic fever in young adults. *Texas State J. Med.* 41: 296-300, Oct. 1945.

9. Wendkos, M. H., and Noll, J., Jr.: Symposium on cardiovascular diseases; survey of rheumatic fever in large station hospital. *M. Clin. North America* 28: 124-147, Jan. 1944.

10. Rutstein, D. D. (Chairman, Committee on Standards and Criteria for programs of care.): Jones criteria (modified) for guidance in diagnosis of rheumatic fever. *Mod. Concepts Cardiovas. Dis.* 24: 291-293, Sept. 1955.

MEDICAL AMBASSADORS

Physicians as a group have a better record in military service than does any that I can think of, chiefly because of the Doctor Draft Law. There are many among you who know whereof I speak. But there are also many and increasingly more young physicians who have not had this experience. More is the pity, because medicine speaks a universal language, and the physician is in consequence the best ambassador of goodwill. There are many outlets in foreign lands through which any number of our young physicians could find such experience. Let me cite only a single small but very important one: there ought to be an American physician in every American Embassy of the world. Yet today not half-a-dozen physicians are so stationed.

—RICHARD A. KERN, M. D.
in *Annals of Internal Medicine*
pp. 238-239, Aug. 1958

CARCINOMA OF THE CERVIX

Incidence in Relation to Clinical Findings

WILLIAM H. KERN, *Captain, MC, USAR*
JOHN W. MOOSE, *Captain, MSC, USAR*
ROBERT I. BOSMAN, *Major, MC, USA*

EXFOLIATIVE CYTOLOGY of the female genital tract has become firmly established as an effective means of cancer detection, and the literature on the subject is extensive. While there is no argument over the value of the cytologic screening procedures, the results concerning the numbers and percentages of positive smears and subsequently detected malignancies, as reported from different medical centers, vary considerably. The reported incidence of carcinoma of the cervix ranges from as low as 2.5 to as high as 11.8 per 1,000 women examined.[1,2] These findings are influenced by the type of the particular segment of population examined, by the use of the cytologic examination as a screening or as a selective diagnostic procedure, and by the histologic criteria used for arriving at a diagnosis of carcinoma in situ. The uncertainty surrounding the microscopic diagnosis of carcinoma in situ makes an evaluation and comparison of series of examinations difficult.[3,4] This applies to the reported incidence of carcinoma as well as to the reported accuracy of the cytologic diagnosis, liberal criteria in the microscopic diagnosis of carcinoma in situ obviously reducing the percentage of false positive cytologic diagnoses.

This study was undertaken in order to determine the incidence, respectively the rate of detection, of carcinoma of the cervix in our own material. The population group examined is unique, most of the women being wives of service personnel or female service personnel, and the average age of this group is younger than that in most comparable series. At the same time, we tried to determine the incidence of pelvic malignant disease in relation to the symptoms and to the clinical appearance of the patients.

From Fifth U. S. Army Medical Laboratory, St. Louis, Mo. Dr. Kern is now at Clinical Laboratory, 679 South Westlake Ave., Los Angeles, Calif.

MATERIAL AND METHODS

During the period from 1 February 1953 to 10 April 1958, cervical and vaginal smears from 8,465 patients were examined at this laboratory. These cases were submitted from station hospitals, dispensaries, and other Armed Forces medical facilities throughout the Fifth U. S. Army Area, which includes 13 states. Most of the patients were dependents of service personnel, but there were also many female members of the armed services. The great majority of the smears was taken as a routine screening procedure. In tabulating these results, the patients were grouped according to the clinical history and the physical findings in order to determine whether detected lesions could be correlated with the clinical appearance. Criteria used for placing the patient in the different groups, the total numbers of patients, and their average age are shown in table 1. In instances where there were both symptoms and physical findings, the patients were placed according to the latter.

TABLE 1. *Criteria used and average age of five groups of patients studied*

Group	Criteria	Number of patients	Average age (years)
I	Routine smears. No symptoms. Clean cervix.	5,210	37
II	Physical findings, described as: erosion, polyp, laceration, granularity, leukoplakia, cysts	1,515	34
III	Symptoms, described as: vaginal discharge, vaginal spotting, chronic cervicitis, metrorrhagia, contact bleeding	1,311	35
IV	Pregnant patients	349	26
V	Carcinoma of the cervix, previously diagnosed, treated in the past by radiation or hysterectomy	80	38

The cases were classified and reported as groups I through V, the criteria being those given by Papanicolaou.[5] For practical purposes, groups III, IV, and V were regarded as being positive, and additional smears or biopsies were recommended.

Table 2 shows the total numbers as well as the percentages of positive smears for patients in the groups defined above. Also shown are all cases of atypical squamous hyperplasia, atypical squamous metaplasia, and leukoplakia, combined under the heading "Atypia"; the cases of carcinoma in situ; and invasive carcinoma. Our criteria for a diagnosis of carcinoma

TABLE 2. *Cytologic findings in 8,465 patients*

Group	Number of patients	Positive smears		Diagnosis		
		Number	Per cent	Atypia*	Carcinoma in situ	Invasive carcinoma
I	5,210	26	0.5	7	4	1
II	1,515	39	2.6	6	4	2
III	1,311	34	2.6	2	4	0
IV	349	2	0.6	0	0	0
V	80	3	3.8	0	0	0
Total, all categories	8,465	104	1.2	15	12	3

*Atypical squamous hyperplasia, atypical squamous metaplasia, and leukoplakia.

in situ are strict and some of our cases of atypical squamous metaplasia or atypical hyperplasia could be classified as carcinoma in situ if more liberal criteria were used.

The total numbers and percentages of carcinoma in situ and invasive carcinoma discovered in each group are given in table 3.

TABLE 3. *Incidence of carcinoma in 8,465 patients*

Group	Number of patients	Number of patients with carcinoma	Rate per 1,000
I	5,210	5	1
II	1,515	6	4
III	1,311	4	3
IV	349	0	0
V	80	0	0
Total	8,465	15	1.8

DISCUSSION

The number of cases of carcinoma found per 1,000 patients examined is lower in our series than in most reports. The fact that strict criteria for a diagnosis of carcinoma in situ were used probably contributed to these results, but we believe that the more important factors were the relatively low average age of our patients and a relatively high percentage of single female service personnel in the series. While the percentage of cases of carcinoma detected per positive smears is essentially the same in the different groups, there is a significant difference

in the incidence of carcinoma for the total number of patients examined in each group. Of the over 5,000 women in group I, with an average age of 37 years who had no symptom and who had a completely normal appearing cervix, the incidence of carcinoma of the cervix was only 1 per 1,000. On the other hand, in both groups II and III, consisting of the women with either symptoms or positive clinical findings, the incidence of carcinoma of the cervix was between 3 and 4 per 1,000. The number of detected carcinomas in each group was small, but it is to be noted that in close correlation to the cases of carcinoma, the number of positive smears is similarly approximately five times greater for groups II and III than for group I. No carcinomas were found in follow-up examinations after treatment or in pregnant women, but too few patients were in these groups to make the findings significant. From these results one may conclude that, while cytologic examinations are a most valuable screening procedure, the chances of finding suspicious or malignant cells on smears and of discovering a carcinoma are approximately three to four times greater in patients who have either symptoms or physical findings related to the genital tract.

SUMMARY

The results of cytologic examinations of the female genital tract on 8,465 women are reported. The incidence of carcinoma of the cervix was found to be 1 per 1,000 in patients with a negative history and no remarkable physical findings at the time the smears were taken. The incidence was between 3 and 4 per 1,000 in patients with positive physical findings or a history of symptoms related to the genital tract. The over-all low incidence of carcinoma as compared to other surveys is attributed to the select nature of the group examined. The history and the physical findings certainly should not be used to determine which patient should be examined by cytologic methods, but a higher incidence of positive findings can be expected if there are symptoms or if there are visible lesions in the cervix.

REFERENCES

1. Day, E.: Value and shortcomings of cytology in uterine cancer control. In *Transactions, First International Cancer Cytology Congress,* Chicago, Ill., Oct. 8-11, 1956. pp. 29-36.

2. Breen, J. L.; Riva, H. L.; and Pickhardt, W. L.: Exfoliative cytology in detection of pelvic malignancy. *U. S. Armed Forces M. J.* 9: 167-171, Feb. 1958.

3. Siegler, E. E.: Microdiagnosis of carcinoma in situ of uterine cervix; comparative study of pathologists' diagnoses. *Cancer.* 9: 463-469, May-June 1956.

4. Taylor, E. S., and Walker, L. C.: Preinvasive cancer of uterine cervix. *Postgrad. Med.* 23: 105-108, Feb. 1958.

5. Papanicolaou, G. N.: *Atlas of Exfoliative Cytology.* Published for the Commonwealth Fund. Harvard University Press, Cambridge, Mass., 1954.

PERICARDIAL CYSTS AND DIVERTICULA

ROBERT J. FLEISCHAKER, *Commander, MC, USN*
JOSEPH J. TIMMES, *Captain, MC, USN*
ROMULUS L. MAY, *Captain, MC, USN*

PERICARDIAL CYSTS and diverticula are benign, relatively rare structures that seldom produce symptoms or cause signs detectable by physical examination. X-ray studies of the chest, including fluoroscopy, tomography, and use of induced pneumoperitoneum, may enable the discovery, delineation, and localization of an abnormal structure in the vicinity of the pericardium but do not provide an accurate differentiation of a cyst or diverticulum from a malignant neoplasm. It is chiefly this difficulty of establishing an accurate diagnosis that has stimulated continuing surgical interest in these lesions. Five cases treated surgically during the past eight years are presented below.

CASE REPORTS

Case 1. A 31-year-old warrant officer developed cough, fever, and malaise. Under treatment with bed rest and penicillin, his symptoms subsided completely within a few days. Serial roentgenograms of the chest, however, revealed a persistent density just above the diaphragm at the left border of the cardiac shadow. Fluoroscopy localized this lesion anteriorly. The structure transmitted pulsations of the heart. Results of physical examination and routine laboratory studies were normal. A left thoracotomy was performed through the fifth intercostal space, and a thin-walled, translucent cyst, 4 by 3 by 3 cm, attached by a fibrous pedicle to the pericardium anterior to the phrenic nerve, was excised. No definite opening of the cyst into the pericardial sac was demonstrated. The excised lesion was a unilocular cyst, containing a yellowish, cloudy fluid. The wall was thin and fibrous, with a lining of flattened epithelial-like cells. Scattered collections of lymphocytes were found in the wall. The postoperative course was uneventful, and the patient was restored to full duty.

Case 2. A 25-year-old man was asymptomatic, but a routine roentgenogram of the chest disclosed a density adjacent to the right cardiac border, just above the diaphragm. Further roentgenograms, including a study using induced pneumoperitoneum, more clearly delineated the mass and localized it anteriorly (figs. 1 and 2). Results of physical

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From U. S. Naval Hospital, St. Albans, N. Y.

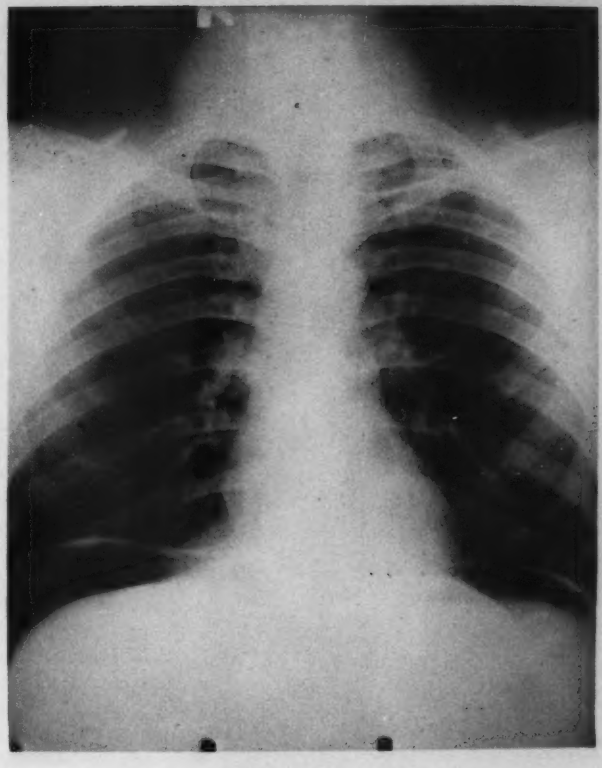

Figure 1 (case 2). Posteroanterior chest roentgenogram, with induced pneumoperitoneum, demonstrating mass in right cardiophrenic angle.

examination and routine laboratory studies were essentially normal. An upper gastrointestinal series of roentgenograms, barium enema roentgenograms and intravenous urography were normal. Bronchoscopy was negative. A thoracotomy was performed, with subperiosteal resection of the sixth right rib. The lesion was found to be a thin-walled cyst, attached to the pericardium. No continuity of the cyst lumen with the pericardial sac was found. The cyst was excised without difficulty. It was 6 by 5 by 3 cm in size, with a thin, translucent wall, and was filled with serous fluid. The inner surface of the wall was bright, shining white, with irregular trabeculations and overlapping of the membranes, giving a multilocular appearance. On microscopic study, the wall was found to be composed of edematous collagenous connective tissue and fat, with a lining of flat "mesothelial" cells. The postoperative course was uncomplicated, and the patient returned to full duty.

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Figure 2 (case 2). Right lateral chest roentgenogram, showing mass anteriorly in right costophrenic angle.

Case 3. A 21-year-old man came to medical attention because of an acute respiratory infection, which subsided promptly with symptomatic therapy. Serial roentgenograms of the chest, however, revealed a persistent mass in the left cardiophrenic angle. Further roentgenograms localized the mass anteriorly. Results of physical examination and routine laboratory studies were essentially normal. Through a left thoracotomy, a thin-walled cyst, attached to the pericardium, was excised. In this case there did appear to be communication of the cyst lumen, through the pedicle, with the pericardial sac. The mass was 2.5 by 2 by 2.5 cm. Its wall was 0.1 cm thick. The structure was unilocular, with a smooth, glistening lining that varied from pink to gray-pink. Microscopic study showed the lining to be a layer of flattened "epithelial" cells. The wall was hyalinized connective fibrous tissue, which was infiltrated in some areas by "round cells." The postoperative recovery was uneventful. The patient returned to full duty.

Case 4. A 20-year-old man was hospitalized because of an abnormality seen in a routine chest roentgenogram. He had no complaints, and the physical examination was essentially normal. All laboratory studies were within a normal range. Roentgenographic studies of the chest demonstrated a globular lesion at the right cardiophrenic angle, not sharply defined, but measuring roughly 3 by 4 cm. Lateral films localized this lesion anteriorly. Tomography did not add to this information. An upper gastrointestinal roentgenographic series and barium enema roentgenograms were essentially normal. At operation through a right thoracotomy, a translucent cyst, 2 by 3 cm, was encountered at the pericardium, adjacent to the crossing of the phrenic nerve. The cyst was removed with ease and detached from a thin, fibrous stalk, which was attached to the pericardium. Patency of this stalk could not be determined. The cyst was unilocular. The postoperative course was uneventful and the patient was returned to full duty.

Case 5. A 23-year-old first class petty officer was discovered by routine chest roentgenography to have a density at the right cardiophrenic angle. For several years he had had a slight cough in the mornings. It was productive of only a few ml of mucoid sputum daily. Physical examination was negative. Routine laboratory studies were all within normal limits. Multiple roentgenographic studies of the chest, including tomography and the use of induced pneumoperitoneum, further delineated and localized the lesion anteriorly at the right costophrenic angle (figs. 3 and 4). Some of the films suggested the possibility that the lesion was a hernia through a foramen of Morgagni. An upper gastrointestinal series of roentgenograms and a barium enema study were normal, however. Thoracotomy through the right sixth intercostal space revealed the lesion to be a thin-walled, translucent diverticulum of the pericardium. This structure, 5 by 4 by 4 cm, was attached to the pericardium by a narrow stalk, through which there was free communication with the pericardial sac. Pressure on the diverticulum would empty its fluid contents into the pericardial sac. The diverticulum was easily excised. It was a unilocular, cystic lesion with a thin, fibrous wall, lined by a single layer of flattened, epithelial-like cells (fig. 5). The postoperative recovery was uncomplicated, and the patient returned to full duty.

DISCUSSION

Since 1934, when Pickhardt[1] reported the first successful surgical excision of a cyst adjacent to the pericardium, several small series of such cases have been reported. Blades,[2] in 1946, reported 10 pericardial cysts as part of a series of 109 mediastinal tumors collected from five U. S. Army hospitals during World War II. Bradford, Mahon, and Grow[3] reported eight cases in 1947. Drash and Hyer,[4] in 1950, reported five cases from the University of Virginia, and discussed 16 others from the literature. Lillie, McDonald, and Clagett[5] reported 12 cases from the files of the Mayo Clinic, and reviewed 25 others collected from the literature

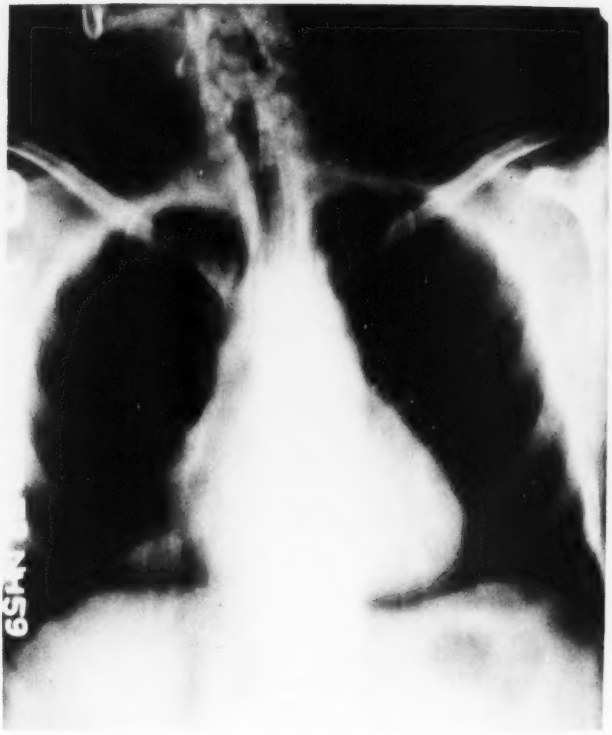

Figure 3 (case 5). Posteroanterior tomogram demonstrating mass anteriorly in chest, at the right cardiophrenic angle.

up to 1950. Davis, Dorsey, and Scanlon[6] reported two cases in 1953. Other similar reports are to be found in the literature.[7-11]

In many instances, these lesions have been asymptomatic. In some cases, however, patients had cough, dyspnea, pleuritic type of pain, substernal pain, a sense of precordial pressure, tachycardia, or "fluttering" of the heart. It seems reasonable that the local pressure of a large cyst might cause such symptoms.

Characteristically, these lesions are thin-walled cystic structures. Usually they are unilocular. The wall is composed of fibrous connective tissue, lined by a single layer of flattened cells resembling serosal or endothelial cells. The cysts usually contain a clear, colorless or yellowish fluid, with physical and chemical properties suggestive of a transudate. These lesions are most common in one of the cardiophrenic angles, adjacent to the anterior chest wall; more of them occur in the right cardio-

Figure 4 (case 5). Right lateral chest film with induced pneumoperitoneum, delineating mass anteriorly in right costophrenic angle.

phrenic angle than in the left one. However, they can occur elsewhere in the mediastinum, adjacent to the pericardium.

The origin and precise nature of these cystic structures is obscure. A widely accepted theory of their origin is that advanced by Lambert,[7] who stated that in the development of the pericardium, in embryonic life, a series of disconnected lacunae appear in the mesenchyme. These enlarge, gradually merge and form the pericardial coelom. Failure of one of these lacunae to merge with the others results in cyst formation. Other possible developmental sources of a cyst in the vicinity of the pericardium are: (1) a pinched-off fold of pericardium; (2) a pinched-off fold of pleura; and (3) a lymphogenous cyst. Actually, it seems probable that several types of cystic lesions may exist in the vicinity of the pericardium. Lymphogenous cysts (cystic hygromas) may be differentiated by a tendency to a multilocular character, by the presence of elastic tissue and smooth muscle in the cyst

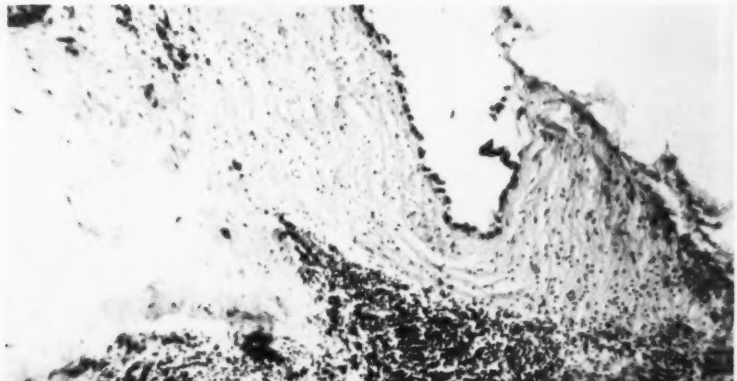

Figure 5 (case 5). Photomicrograph of wall of diverticulum showing a localized collection of lymphocytes. (× 200)

wall, and by the frequent association of smaller dilated lymphatic channels.[12] Maier[11] has reported pericardial diverticula that appeared to be of acquired origin, presumably the result of increased pressure within the pericardial sac during a pericardial effusion.

The establishment of an accurate diagnosis is of great practical importance. Thymic cysts and tumors, teratomas, lipomas, and parasitic cysts can mimic the roentgenographic appearance of a pericardial cyst. Also, it may be difficult by roentgenographic studies, to differentiate a hernia through a foramen of Morgagni from a pericardial cyst. In the final analysis, surgical exploration is required to establish the diagnosis with certainty.

SUMMARY

Three pericardial cysts and two pericardial diverticula, all of which were discovered by roentgenograms of the chest, are reported. The differential diagnosis includes several types of mediastinal cysts and tumors, some of which may be malignant, and a hernia through a foramen of Morgagni. Because of the necessity of ruling out a malignant lesion, the therapy of pericardial cysts and diverticula requires surgical exploration and excision.

REFERENCES

1. Pickhardt, O. C.: Pleuro-diaphragmatic cyst. In Transactions of New York Surgical Society, held Apr. 12, 1933. *Am. Surg.* 99: 814-816, May 1934.

2. Blades, B.: Mediastinal tumors; report of cases treated at Army Thoracic Surgery Centers in the United States. *Am. Surg.* 123: 749-765, May 1946.

3. Bradford, M. L.; Mahon, H. W.; and Grow, J. B.: Mediastinal cysts and tumors. *Surg. Gynec. & Obst.* 85: 467-491, Oct. 1947.

4. Drash, E. C., and Hyer, H. J.: Mesothelial mediastinal cysts; pericardial celomic cysts of Lambert. *J. Thoracic Surg.* 19: 755-768, May 1950.

5. Lillie, W. I.; McDonald, J. R.; and Clagett, O. T.: Pericardial celomic cysts and pericardial diverticula; concept of etiology and report of cases. *J. Thoracic Surg.* 20: 494-504, Sept. 1950.

6. Davis, C., Jr.; Dorsey, J. M.; and Scanlon, E.: Cysts about pericardium. *A. M. A. Arch. Surg.* 67: 110-121, July 1953.

7. Lambert, A. V.: Etiology of thin-walled thoracic cysts. *J. Thoracic Surg.* 10: 1-7, Oct. 1940.

8. Weig, C. G., and Fuge, W. W.: Pericardial coelomic cyst. *Dis. Chest* 26: 110-116, July 1954.

9. Forsee, J. H., and Blake, H. A.: Pericardial celomic cyst. *Surgery* 31: 753-760, May 1952.

10. Brown R. B., and Dunn, R. G.: Lymphogenous cysts of mediastinum; cystic hygromas, pericardial cysts, and pericardial diverticulums. *U. S. Armed Forces M. J.* 2: 1651-1667, Nov. 1951.

11. Maier, H. C.: Diverticulum of pericardium with observations on mode of development. *Circulation* 16: 1040-1045, Dec. 1957.

12. Lindskog, G. E., and Liebow, A. A.: *Thoracic Surgery and Related Pathology.* Appleton-Century-Crofts, Inc., New York, N. Y., 1953. p. 534.

CURATIVE EFFECT OF CLAIMS SETTLEMENTS

"One hundred patients with previously diagnosed cervical neck strain following auto accidents whose litigation on compensation claims had been settled were queried as to their present clinical status. After legal claims for damage were completed, 88 per cent showed recovery, and over half of these had no residual complaints. Many emotional factors, but especially those concerning monetary compensation, greatly confuse proper medical evaluation and appear to be the cause of the wide divergence of professional prognostic opinions relative to this particular injury."

—NICHOLAS GOTTEN, M. D.
in *Journal of the American Medical Association*
p. 865, Oct. 27, 1956

THE PARTIAL MASKING OF ANEMIA BY CONTRACTED BLOOD VOLUME

WILLIAM H. CROSBY, *Lieutenant Colonel, MC, USA*

ANEMIA is often suspected from a patient's appearance and confirmed by measuring the concentration of hemoglobin in his blood. The hemoglobin values of normal people are usually between 12 and 16 grams per 100 ml of blood, the hematocrit 40 to 50 per cent, and anemia is often defined as the state in which the hemoglobin or hematocrit is lower than normal. Now methods are available for measuring the size of the mass of circulating red blood cells, and we are learning to define anemia in terms of milliliters of red cells per kilogram of body weight. Total mass of circulating red blood cells in normal people is usually between 26 and 33 ml per kg of body weight. Women have less red cells per kg than men;[1] and, because adipose tissue is poor in blood, obese people have fewer red cells than thin ones.[2]

These interesting studies have revealed that the concentration of hemoglobin in the blood is not always a true index of the total amount of hemoglobin. It is well known that, for example, after a severe hemorrhage the blood volume may be reduced by one or two liters but for a time the concentration of hemoglobin remains unchanged. Less obvious examples of a lack of correlation have been demonstrated in pregnancy, where it has been shown that the "physiological anemia of pregnancy" may be due to an increase of plasma volume rather than a reduction of red cells.[3] The same "hemodilution" may occur in advanced cirrhosis.[4] In polycythemia vera the total blood volume is expanded as well as the red cell volume.[5] The total red cell mass may be more than doubled (e. g., from 30 ml per kg of body weight, it may increase to 75 ml) but the hematocrit in the same patient may increase by only one half. From 45, the hematocrit may increase to 70 per cent.

This article calls attention to one of the consequences of severe anemia on the blood volume, and the clinical significance of this phenomenon is commented on.

From Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

MATERIALS AND METHODS

The study involved measurement of the red blood cell mass and the venous hematocrit of a number of normal subjects and patients with severe anemia. Thirty-four soldiers, participating in various transfusion studies in this department, comprised the control group. All were in good health with normal habitus. Thirty-one patients included in the study were among those admitted to the hematology service of Walter Reed Army Hospital. We have not included any patients who were pregnant or suffering from cirrhosis, or malignant disease with cachexia. The diagnoses are shown in figure 1.

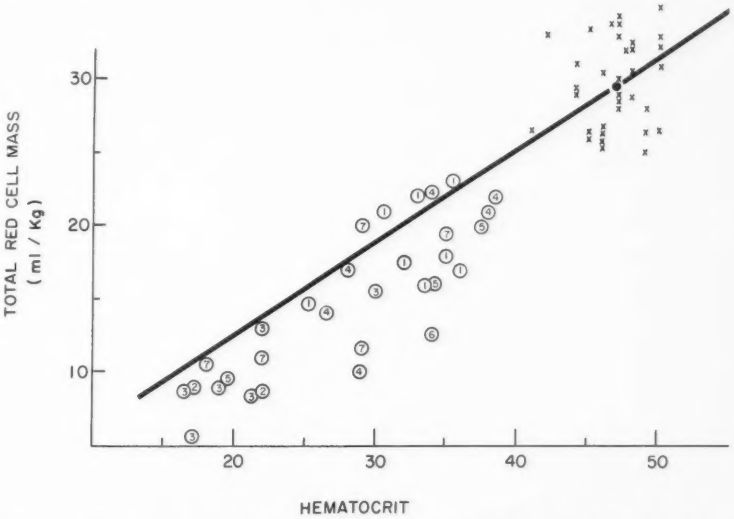

Figure 1. The partial masking of anemia by reduction of the total blood volume. The solid dot represents the average hematocrit (46.8 per cent) and the average red blood cell mass (29.7 per cent) of 34 normal subjects. The averages were divided one into the other to determine that every hematocrit point represents 0.635 ml per kg of circulating red cells. Using this value the line was drawn to demonstrate the corresponding volume of red cells for every hematocrit value. The line also represents values for hematocrit and red cell volume that would be obtained when the total blood volume remains constant and a quantity of plasma is substituted for an equal quantity of red cells. Notice that in every case of severe anemia the point falls below this line. This indicates that the total blood volume is diminished: The plasma did not expand sufficiently to compensate entirely for the reduction of the red cell mass. The distance of any point from the line is a measure of the amount by which the hematocrit value fails to reflect the actual reduction of the red cell mass. The patients are divided into 7 diagnostic groups, indicated by an encircled number: (1) iron deficiency anemia; (2) pernicious anemia; (3) aplastic and refractory anemia; (4) hereditary anemia including spherocytosis, thalassemia and nonspherocytic hemolytic anemia; (5) acquired hemolytic anemia; (6) paroxysmal nocturnal hemoglobinuria, and (7) chronic leukemia.

Red blood cell mass was measured by the transfusion of a measured volume of red cells tagged with radioactive chromium (Cr^{51}). The red cell mass was computed by determining the extent to which the Cr^{51} was diluted after it had mixed with the entire amount of circulating blood.[6] The values are stated in terms of milliliters of circulating red cells per kilogram of body weight.

The hematocrit was measured in capillary tubes, spun on a high-speed centrifuge.[7] The values are stated in terms of packed red cells to the per cent of whole blood, or as ml per 100 ml.

RESULTS

The 34 normal subjects were found to have an average hematocrit of 46.8 with a range from 41 to 50. Their red cell mass averaged 29.7 ml per kg of body weight with a range from 25.5 to 35 ml. The distribution is shown in figure 1. The averages indicate that there were 0.6 ml of circulating red cells for every hematocrit point. Using this value, a line was drawn on figure 1 representing the corresponding value of circulating red cell mass for every hematocrit point between 15 and 55.

The 31 patients represented in figure 1 were those with a red cell mass less than 23 ml per kg. The average red cell mass of the group was 14.9 ml with a range from 5.4 ml to 22.5 ml per kg. The average hematocrit was 28.3 with a range from 16.5 to 38.5. The wide scatter of the values around the average is shown in figure 1 where each patient is represented by a number referring to his diagnosis. When we treat the averages, as we did those of the normal group, it is found that there are 0.5 ml of circulating red cells for every hematocrit point, a deviation from the normal average amounting to 17 per cent. The hematocrits of the anemic patient indicate anemia of less severity than do the corresponding values for the red cell mass. When plotted on the graph in figure 1 the points lie below the line which represents the normal relationship of hematocrit to red cell mass (0.6 ml of red cells for every hematocrit point). This abnormality is sometimes called "hemoconcentration."

To demonstrate what happens to the blood and red cell volumes in severe anemia let us select some arbitrary value as an example. Consider a hypothetical healthy man whose total blood volume is 70 ml per kg of body weight, of which the red cell mass is 30 ml and plasma volume is 40 ml. His venous hematocrit is 48 per cent.* This hypothetical man develops

*A distinction is made between venous hematocrit (the hematocrit of blood taken from a large vein) and the body hematocrit (the proportion of red cells to plasma in the entire blood volume). The body hematocrit is about 90 per cent of the venous hematocrit. Even in the presence of severe anemia, the ratio of venous hematocrit to body hematocrit remains about 0.90.[8] In this hypothetical healthy man the body hematocrit is 30/70 or 43 per cent.

aplastic anemia and, when we measure his blood volume again, the red cell mass is 10 ml, the plasma volume 50 ml, and the total blood volume 60 ml per kg. The plasma volume has increased to compensate for the loss of red cells, but it has not increased enough to provide a total blood volume equal to the initial 70 ml. The venous hematocrit is now 24. The total red cell mass is decreased by two-thirds, but the hematocrit is decreased by only one-half. In terms of circulating red blood cells per hematocrit point, the initial value is 0.6 ml, the value after anemia develops is 0.4 ml. In several of the patients in figure 1 values as low as 0.3 ml were found.

Partial Masking of Anemia

In clinical terms this means that in severe anemia the lack of red blood cells is worse than it would seem to be when one uses the hematocrit or hemoglobin concentration as the parameter of severity. It is significant that this partial masking of anemia was present in all of the patients whose red cell mass was less than 20 ml per kg. The range of aberration was wide (fig. 1). All of the points are below the line that represents the "normal" volume of circulating red blood cells per hematocrit point. Some are close to the line; others are far away. Consider, for example, patient number 6 with nocturnal hemoglobinuria. His hematocrit was 34. If his red cell mass had been represented proportionately by the hematocrit it would have been 22 ml per kg; it actually was 12 ml.

This partial masking of anemia was also found in severely wounded soldiers who were studied in Korea (fig. 2). These men had been given large transfusions of blood during the process of resuscitation and surgery. When hematocrits were done afterward the results seemed fairly satisfactory but measurement of the red cell mass with Cr^{51}-tagged red cells revealed that the mass of circulating red cells was disproportionately low.[9] In these patients dehydration may have been partially responsible for the hemoconcentration.

In patients with chronic severe anemia, dehydration does not play a part although there is hemoconcentration, which we have referred to as partial masking of anemia. When the red cell mass becomes quite small, as it does in severe anemia, there are at least two important disturbances in the function of the blood. The total blood volume is diminished, thus impairing the efficiency of the circulation, and the oxygen-carrying capacity of the blood is reduced. The compensatory alteration of the plasma volume may be regarded as a compromise: the increase of plasma partially restores the blood volume, but it causes a further dilution of the oxygen capacity. The moderate hemoconcentration benefits the oxygen capacity at the expense of the total blood volume. The partial masking of anemia may represent a protective mechanism of this sort.

It is not the purpose of this report to recommend measuring the red cell mass instead of the hemoglobin concentration to diagnose anemia, because severe anemia can be diagnosed by inspection. The patient's reaction to his anemia is a better index of the degree of severity than any blood count.[10] Some patients are incapacitated with a hematocrit of 30 while others are comfortable and fairly active with hematocrits of 15. In this regard, what the patient says and his vital signs (pulse and blood pressure) may be better guides to his condition than the results of either laboratory test, hematocrit, or red cell mass.

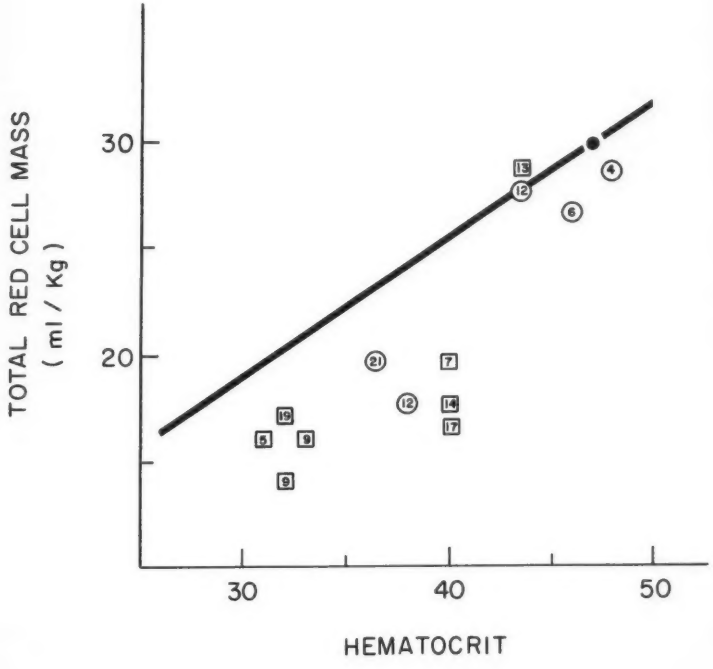

Figure 2. The partial masking of anemia by "hemoconcentration" in severely wounded battle casualties. This figure was constructed from data published by Prentice and his associates.[9] The line is the same as that in figure 1. Each case is represented by a number which is the number of liters of blood he received during the resuscitation and surgery immediately before the blood volume was measured. A large transfusion is indicative of a very severe wound. The squares represent wounds of the extremities, and the circles are abdominal wounds. These patients have acute anemia as contrasted with the chronic anemia demonstrated in figure 1. But, as in figure 1, the points representing severe anemia fall below the "normal" line. A reduced red blood cell mass is associated with a reduced total blood volume.

SUMMARY

In severe anemia the total red blood cell mass is reduced to a greater extent than the venous hematocrit. This disproportion is caused by diminution of the *total* blood volume when the red cell mass becomes very small. In the acute anemia associated with severe injury, this phenomenon may be aggravated by dehydration. In chronic anemia it may reflect an effort to maintain the oxygen capacity of the blood by maintaining the hemoglobin concentration at the expense of the total blood volume.

REFERENCES

1. Wadsworth, G. R.: Blood volume of normal women. *Blood* 9: 1205-1207, Dec. 1954.

2. Huff, R. L., and Feller, D. D.: Relation of circulating red cell volume to body density and obesity. *J. Clin. Invest.* 35: 1-10, Jan. 1956.

3. Verel, D.; Bury, J. D.; and Hope, A.: Blood volume changes in pregnancy and puerperium. *Clin. Sc.* 15: 1-7, Feb. 1956.

4. Eisenberg, S.: Blood volume in patients with Laennec's cirrhosis of liver as determined by radioactive chromium-tagged red cells. *Am. J. Med.* 20: 189-195, Feb. 1956.

5. Dameshek, W.: Physiopathology and course of polycythemia vera as related to therapy. *J. A. M. A.* 142: 790-797, Mar. 18, 1950.

6. Hollingsworth, J. W., and Hollingsworth, D. R.: Study of total red cell volume and erythrocyte survival using radioactive chromium in patients with advanced pulmonary tuberculosis. *Am. Int. Med.* 42: 810-815, Apr. 1955.

7. Houchin, D. N.; Lamanna, A. L.; and Lambert, M.: Improved technic for capillary hematocrit determination. *M. Tech. Bull.* 6: 171-173, July-Aug. 1955.

8. Chaplin, H., Jr.; Mollison, P. L.; and Vetter, H.: Body/venous hematocrit ratio: its constancy over wide hematocrit range. *J. Clin. Invest.* 32: 1309-1316, Dec. 1953.

9. Prentice, T. C.; Olney, J. M., Jr.; Artz, C. P.; and Howard, J. M.: Studies of blood volume and transfusion therapy in Korean battle casualty. *Surg. Gynec. & Obst.* 99: 542-554, Nov. 1954.

10. Crosby, W. H.: Misuse of blood transfusion. *Med. Bull. U. S. Army Europe* 15: 3-4, Jan. 1958.

WHAT THE AUTHOR MEANT

Here is a sentence from a medical journal: "Experiments are described which demonstrate that in normal individuals the lowest concentration in which sucrose can be detected by means of gustation differs from the lowest concentration in which sucrose (in the amount employed) has to be ingested in order to produce a demonstrable decrease in olfactory acuity and a noteworthy conversion of sensations interpreted as a satiety associated with ingestion of food." All the author meant was: Experiments are described which show that normal people can taste sugar in water in quantities not strong enough to interfere with their sense of smell or take away their appetite.

—RICHARD ASHER, M. D.
in *British Medical Journal*
p. 503, August 23, 1958

AIR-FLOW OBSTRUCTION IN ALLERGIC ASTHMA AND ITS EFFECT ON THE LUNG COMPARTMENTS

An Analysis of Lung Compartment Relationships in 42 Cases

JAMES C. SYNER, *Major, MC, USA*

OBSTRUCTION to air flow within the bronchial tree has been designated as the principal abnormality in the pathogenesis of obstructive emphysema.[1-5] The anatomic counterpart of the functional air-flow impairment is bronchial obstruction or bronchospasm or both. Spain and Kaufman[3] reported on the histopathology of the lung in emphysema and described in detail the anatomic changes which obstruct the lumens of the terminal and respiratory bronchioles. Whether or not bronchospasm forms a physical basis for air-flow obstruction will not be discussed in this report. Suffice it to mention that some authors believe that at the present there is no factual evidence for the existence of bronchospasm in the bronchial tree.[6]

The proponents of bronchiolar obstruction further contend that air-flow impairment, by establishing a state of air trapping, produces hyperinflation of the alveoli which eventually leads to mechanical overdistension of the lungs. The distended alveoli effect an impairment in the blood and oxygen supply which produces further advances in the degenerative changes of tissue atrophy and disruption. This state of a hyperinflated lung volume with disturbances in lung compartment relationships, impaired blood supply, and tissue atrophy in the presence of air-flow obstruction bears the clinical diagnosis of *obstructive pulmonary emphysema.*

The concept of emphysema developing and progressing from air-flow obstruction is not universally accepted. Rappaport and Mayer[6] stated that, "obstructive bronchitis is more often the result rather than the cause of pulmonary emphysema." It is their concept that emphysematous changes must be present in the lung in order for obstructive bronchitis to occur. These authors believe that emphysema is revealed, not produced, by the signs and symptoms of obstructive bronchitis. Stead, Fry,

From Fitzsimons Army Hospital, Denver, Colo.

and Ebert[7] reported on the elastic properties of the lungs in patients with emphysema and stated, "It is generally accepted that the basic defect of chronic pulmonary emphysema is a loss of the normal retractive forces of the lung." This concept localizes the site of primary change within the alveolar wall. Abbott and associates[8] stated that focal trigger areas of bronchial obstruction may play a primary role in the pathogenesis of emphysema by reflexly stimulated pulmonary arteriolar and bronchiolar spasm via the autonomic nerves. That circulatory occlusive changes of the bronchial arteries may play a primary role in the production of lung atrophy was suggested by Cudkowicz and Armstrong.[9]

PURPOSE OF STUDY

This study was designed to obtain information regarding the role of air-flow obstruction as a precursor and aggravator of obstructive pulmonary emphysema. The basic approach involved relating *duration of air-flow obstruction* to the *severity of alterations in lung compartment relationships,* with particular focus on the size of the functional residual capacity (FRC) and the ratio of residual volume to total lung capacity (RV/TC). If a cause and effect relationship does exist between air-flow obstruction and obstructive emphysema, such a study should provide data essential to its proof.

It was further reasoned that this information would aid in formulating decisions as to the advisability of *accepting* or *retaining* in military service individuals with air-flow obstruction. The data would serve as aids in making a prognosis as to the individual's career and job potential in terms of future functional capacities. In such a perspective, the information has bearing on problems of disability evaluation, and is considered to represent one aspect of a broad-study approach to the evaluation of disability in diseases of the chest through utilization of pulmonary function studies.

MATERIAL AND METHODS

The 42 patients included in this study were diagnosed as having true allergic bronchial asthma. This diagnosis was based on the following criteria:

1. Family history.
2. Allergic equivalents to include:
   (a) Rhinitis, seasonal or perennial.
   (b) Conjunctivitis, seasonal.
   (c) Sneezing.
   (d) Examination of upper respiratory passages demonstrating the characteristic "allergic mucosa."
   (e) Eosinophils of greater than 10 per cent from either sputum, nasal secretions, or blood.

3. Immunologic findings to include multiple positive skin tests.

4. Symptomatic relief obtained by one or more of the following measures:
   (a) Antihistamines.
   (b) Hyposensitization.
   (c) Environmental modifications and controls.

5. Age of onset:
   (a) Early childhood allergies.
   (b) Asthma may appear in later life.

The cases selected in this study satisfied a minimum of any four of the five criteria. All had multiple, highly positive skin tests.

The studies were performed at a time when patients felt "well" and clinically were regarded as asymptomatic or free of the characteristic asthmatic "attack." Patients diagnosed as having true allergic bronchial asthma were admitted to the study for the following reasons:

1. The acute clinical findings and subjective distress, characteristic of the asthmatic "attack," serve as a relatively precise episode for dating the onset of significant air-flow obstruction.

2. The air-flow obstruction in bronchial asthma is a diffuse process involving the entire lung with equal intensity.

3. The acute disabling distress of the "attack" usually demands medical treatment, thereby placing the patient under observation and follow-up management early in the course of the disease.

The advantages of studying the sequelae of air-flow obstruction in true bronchial asthma appears in sharp contrast to the difficulties and uncertainties involved in tracing and identifying etiologic relationships between *air-flow obstruction* and *obstructive emphysema* in the chronic bronchitis syndrome. The clinical course in bronchitis is usually one of insidious progression without an acute, dramatic "attack" from which one can date the probable onset of significant air-flow obstruction. Air-flow obstruction of a marked degree may be present when auscultation of the lungs is regarded as "clear," and when the patient is unaware of any increased work of breathing. As a result of the insidious nature of the disease at this stage, the patient comes to the attention of the physician at a time when advanced emphysema is present. At such time one cannot distinguish chronic bronchitis from obstructive emphysema relative to cause and effect relationships. What portion of the disease complex reflects obstructive bronchitis, and what portion reflects obstructive emphysema, cannot be identified with any reasonable certainty. The identical clinical picture may be described by some as chronic bronchitis, and by others as obstructive

emphysema. Rappaport and Mayer[6] stated as their concept that obstructive bronchitis is usually the effect of obstructive emphysema rather than its cause.

Conventional pulmonary function studies as previously described were performed on each patient.[10-14] These included gross spirometry, calculation of specific flow rates, and measurement of lung compartment volumes and relationships. The functional residual capacity (FRC) is regarded as highly important in quantitating the shift of the midpulmonary position caused by hyperinflation of the lung volume. It has been regarded by some as the principal difference between normal individuals and patients with pulmonary emphysema.[7] It is reasoned that the FRC is determined by the state of balance between the passive forces of the chest wall and the retractive force of the lung. The ratio of residual air to total lung volume (RV/TC × 100) is also regarded as an important diagnostic and quantitative expression of obstructive emphysema. Therefore, the FRC and the RV/TC × 100 were selected as the principal measurements for quantitating the presence and degree of severity of the emphysematous state.

Data on the per cent of predicted normal FRC and the RV/TC × 100 in 30 normal individuals, used as a control group, are presented to describe the distribution of these functions in various ages. These data were included in scattergrams as a convenient means of comparing normals to the patients with bronchial asthma.

RESULTS

The scatter for FRC's (fig. 1) demonstrates that 130 per cent of predicted normal is the approximate upper limit of normal in any age group. The scatter in figure 2 demonstrates a variation in the ratio of residual volume to total lung volume related to age. A rise in the ratio with increasing age is noted, and has been described by Baldwin, Cournand, and Richards.[15] Whereas a ratio of greater than 35 per cent is generally accepted as indicating the presence of a significant degree of emphysema,[15] in its strictest application the ratio must be interpreted in the light of the individual's age in estimating presence and degree of emphysematous changes. The data indicate that the upper limit of normal for this function, for all age groups, is 35 per cent. With the exception of two cases, all normals tested, regardless of age, had a ratio of less than 35 per cent.

In comparing figures 1 and 3 a significant difference is noted between the normal and asthmatic patients. In the group of 42 patients, 2 with perennial and 6 seasonal asthma were within the accepted normal limit of 130 per cent of predicted normal. The remaining 36 patients (85.6 per cent) were abnormal for this function. Although the scatter strongly suggests that airflow obstruction is more traumatic in older patients, especially

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those above 45 years, 3 patients below 40 years of age had an FRC that was greater than 260 per cent of predicted normal. This is considered as a severe degree of expansion for this lung compartment. The scatter also suggests that perennial asthma is more traumatic on this lung compartment than the seasonal type. Of the 14 patients with seasonal asthma, 7 were within normal range, and 7 were abnormal. In the 28 patients with perennial asthma, 3 were normal and 25 were abnormal.

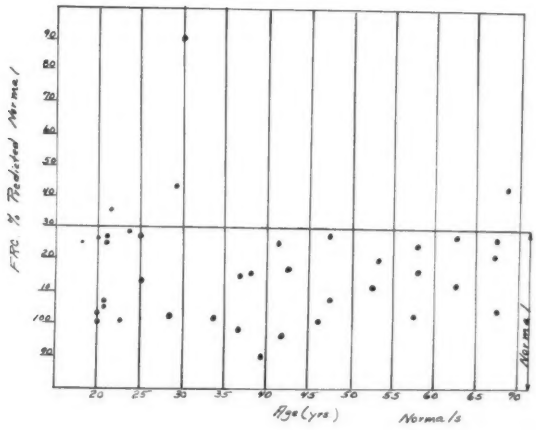

Figure 1. Relationship between the per cent predicted normal functional residual capacity and age in 38 normal individuals. The horizontal line at 130 per cent is regarded as the upper limit of normal.

The data in figures 2 and 4 demonstrate a significant difference between normal and asthmatic patients as regards RV/TC ratio. In the group of 42 asthmatic patients, 12 (28.5 per cent) were normal, whereas 30 (71.5 per cent) were abnormal. In the control group of 30, 95 per cent were within normal limits. The close grouping of patients with seasonal asthma in the 20-to 25-year period, compared with its infrequent appearance beyond this age, suggests that with progression of time the episodic nature of the disease is replaced by perennial chronicity. The scatter further suggests that, as the episodic type of process is replaced by perennial involvement, progression into an abnormal RV/TC occurs.

Figure 5 demonstrates that the FRC in patients with seasonal asthma is less affected by duration of symptoms than in patients with perennial asthma. In 14 patients with seasonal asthma, 7 were within normal limits, where as only 3 (10.7 per cent) of 28 patients with perennial asthma were normal. Four patients with seasonal asthma had symptoms in excess of 15 years. The 3 patients with perennial asthma normal for this function had

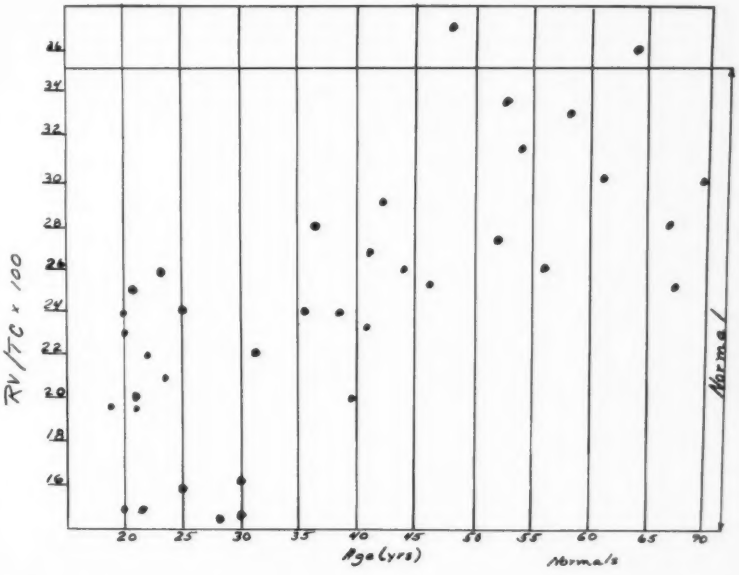

Figure 2. Relationship between the ratio of residual volume to total lung volume (RV/TC × 100) and age in normal individuals. The horizontal line at 35 per cent is taken as the upper limit of normal for all age groups.

symptoms for less than 11 years. In the 17 patients with symptoms of less than 11 years' duration, only 3 had an FRC greater than 170 per cent of predicted normal. The remaining 14 (78.8 per cent) had a normal or only minimally elevated FRC. Twenty-four patients had symptoms in excess of 11 years. Nine of these 24 (37.5 per cent) had a normal or only minimally elevated FRC, whereas 15 (72.5 per cent) had an elevation of the FRC greater than 170 per cent of predicted normal. Eighty-nine per cent of patients with perennial asthma, symptomatic in excess of 11 years, developed an elevation of the FRC greater than 170 per cent of predicted normal.

Figure 6 demonstrates that a significant rise in the FRC occurred with prolongation of symptoms. The figure indicates

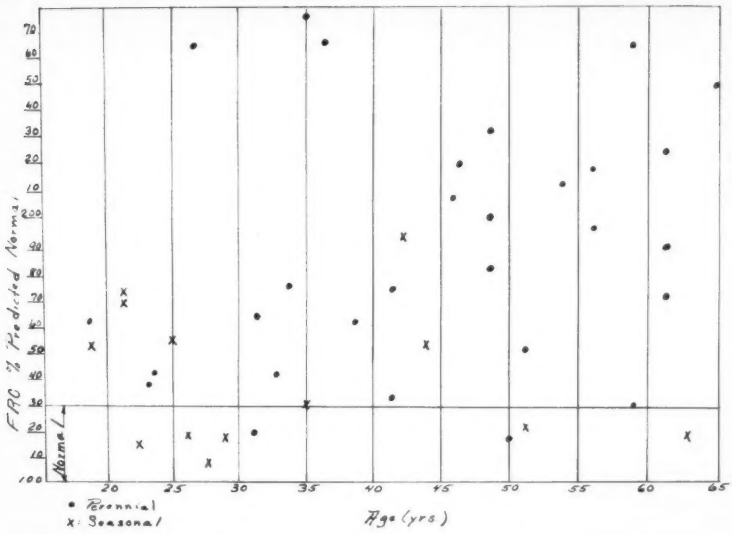

Figure 3. Relationship between the per cent predicted normal functional residual capacity and age in patients with seasonal and perennial asthma. The horizontal line at 130 per cent is regarded as the upper limit of normal.

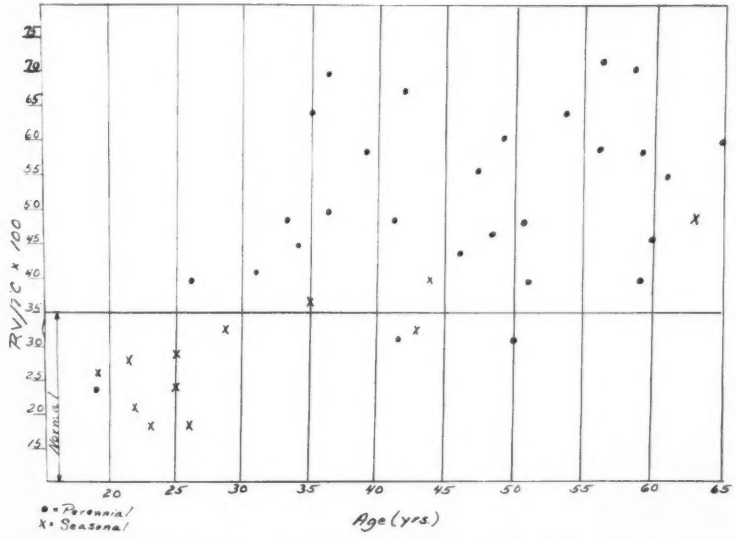

Figure 4. Relationship between the ratio of residual volume to total lung volume (RV/TC × 100) and age in patients with seasonal and perennial asthma. The horizontal line at 35 per cent is regarded as the upper limit of normal.

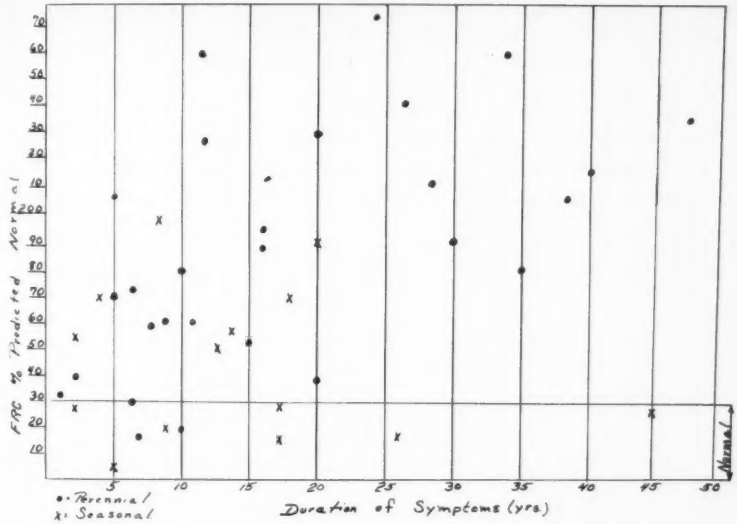

Figure 5. Relationship between the per cent predicted normal functional residual capacity and duration of symptoms in patients with seasonal and chronic asthma. The horizontal line at 130 per cent is regarded as the upper limit of normal.

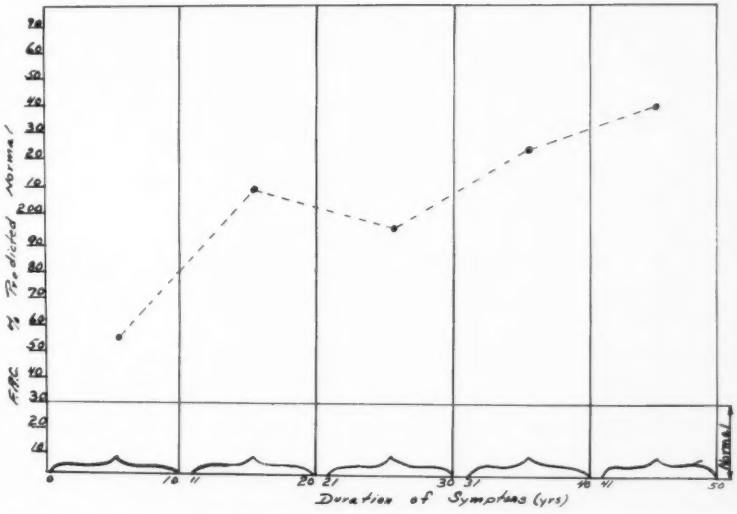

Figure 6. Relationship of the average per cent predicted normal functional residual capacity and the duration of symptoms in patients with perennial asthma. The per cent predicted normal functional residual capacity is the average for the patients exhibting symptoms within the period of time indicated.

that duration of symptoms beyond 10 years resulted in the development of a more severe degree of abnormality in the size of this lung compartment. It indicates that duration of symptoms (air-flow obstruction) carries the risk of producing a degree of hyperinflation that makes it extremely unlikely that any significant degree of reversal in the disturbance can be obtained.

The high degree of scatter demonstrated in figure 7, for the RV/TC, is so great that one may reasonably conclude that this function, unlike the FRC, is not dependent upon duration of symptoms for degree of abnormality. This is consistent with the fact that the RV/TC, unlike the FRC, is dependent upon

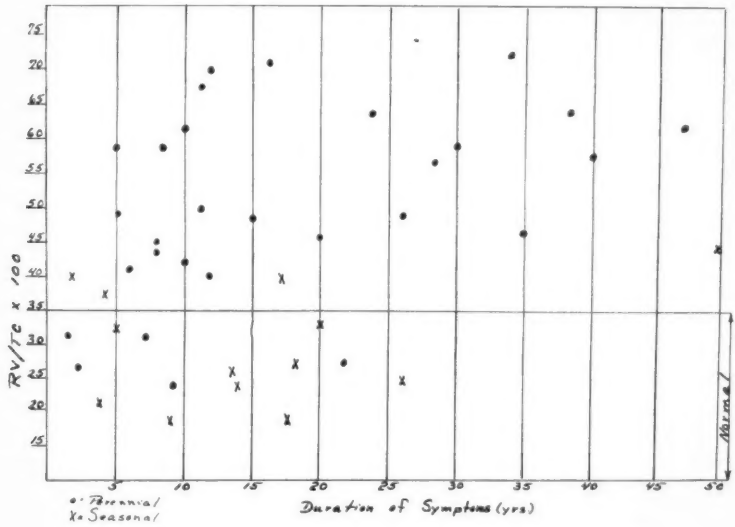

Figure 7. Relationship of the ratio of residual volume to total lung volume (RV/TC × 100) and duration of symptoms in patients with seasonal and perennial asthma. The horizontal line at 35 per cent is regarded as the upper limit of normal.

the expiratory capacity. The expiratory capacity may be highly variable, depending on the nature of the patient's "effort," and the degree of air-flow obstruction. Because the FRC is independent of the patient's expiratory effort, it is free of fortuitous influences.

CONCLUSIONS

A marked increase in the size of the FRC and RV/TC was demonstrated in asthmatic patients during the so-called "asymptomatic" period. These changes were considered to indicate that air-flow obstruction, air trapping, and hyperinflation of the lung volume were present at a time when patients were considered

to be well controlled, and auscultation was entirely to relatively free of wheezes and rhonchi. A relationship was noted to exist between *duration of air-flow obstruction* and *size of the FRC*. Prolongation of air-flow obstruction resulted in a progressive alteration of the lung volume (hyperinflation) characteristic of obstructive emphysema. This relationship was not found to exist between RV/TC and duration of symptoms. An explanation for this was presented.

Seasonal asthma did not result in the degree of abnormality in lung volume relationships that was demonstrated in the perennial variety. The data suggested that seasonal asthma became perennial after 10 to 15 years.

The data strongly suggested that the "golden era" for control of air-flow impairment and prevention of irreversible large lung volume disease was within the first 10 to 15 years following onset of symptoms. Symptoms in excess of 10 years resulted in an elevation of the FRC that was greater than 190 per cent of predicted normal in the vast majority of cases studied (table 1).

TABLE 1. *Mean average for functional residual capacity as per cent of predicted normal according to duration of symptoms*

Duration of symptoms years	Mean average functional residual capacity as per cent of predicted normal
0 to 10	156
11 to 20	214
21 to 30	196
31 to 40	228
41 to 50	240

The evidence indicated that even during the so-called asymptomatic period, significant air-flow obstruction and resultant air trapping and hyperinflation of the lung volume exist in asthmatic patients. This implies the need for continuous medical management. The absence of wheezes and rhonchi in these patients must not be accepted as evidence that air-flow obstruction is not present.

The effect of bronchodilator drugs on the lung compartments in allergic asthma is an important consideration. A basic aim in using these agents is to aid in determining whether bronchospasm with acute hyperinflation or obstructive emphysema is complicating the allergic state. The interpretation of physiologic studies before and after bronchodilator drugs is difficult, controversial, and involves a multiplicity of considerations and variables such as : (1) What degree of change in function after therapy is significant? (2) Which function studies are most sensitive to change following this therapy? (3) Which of several studies shall be regarded as most sensitive in making a differen-

tiation between allergic bronchospasm vs. obstructive emphysema? (4) How shall the medication be administered? (5) How long has the patient used the particular agent and to what degree does he now respond? (6) What is the current state of complicating factors such as infection and air-way congestion with tenacious secretions? In our experience these and other factors enter into the problem of interpretation of pulmonary function studies before and after bronchodilator drugs. Data have been collected and will be reported in a future article.[16]

An important area of this subject is which one of several tests shall be accepted as being most reliable and sensitive for differentiating obstructive emphysema from the acute transient hyperinflation complicating bronchospasm. In identifying the presence of significant alteration in lung compartment relations this article has utilized the FRC. The nitrogen mixing index is preferred by others, especially its measurement before and after bronchodilators. This controversial issue on methodology is difficult to handle without the availability of adequate data. It requires information on the characteristics or frequency distribution of this measurement in normals, and chronic bronchopulmonary diseases other than obstructive emphysema and allergic bronchospasm. Data have been collected on this problem and are now being prepared for publication.[17]

SUMMARY

Pulmonary function studies were performed on 42 patients with true allergic bronchial asthma to evaluate the relationship between *duration of air-flow obstruction* and *alterations in lung volumes*. The functional residual capacity (FRC) and ratio of residual volume to total lung capacity (RV/TC) were the lung volumes selected for study because their seizures are generally considered as most characteristic of the difference between normal men and patients with pulmonary emphysema. The data obtained demonstrated a distinct difference between normal individuals and the asthmatic patients as regards size of the FRC and the elevation of the RV/TC. Interpretation of the data and their clinical significance is presented.

REFERENCES

1. Herschfus, J A.; Bresnick, E.; and Segal, M. S. Pulmonary function studies in bronchial asthma; in control state. *Am. J. Med.* 14: 23-33, Jan. 1953.

2. Phillips, R. W.; Phillips, A. M.; Pauli, A. M.; and Pecora, D. V.: Chronic bronchitis; a neglected disease entity. *Dis Chest* 26: 520-527, Nov. 1954.

3. Spain, D. M., and Kaufman, G.: Basic lesion in chronic pulmonary emphysema. *Am. Rev. Tuberc.* 68: 24-30, July 1953.

4. Kountz, W. B., and Alexander, H. L.: Emphysema. *Medicine* 13: 251-316, Sept. 1934.

5. Laennec, R. T. H.: *Treatise on the Diseases of the Chest and on Mediate Ausculatation.* 3d edition. Translated by J. Forbes, Samuel S and William Wood, New York, N. Y., 1938. p. 152.

6. Rappaport, I., and Mayer, E.: Changing forms and causes of pulmonary insufficiency in present era of medicine. *J. A. M. A.* 165: 431-436, Oct. 5, 1957.

7. Stead, W. W.; Fry, D. L.; Ebert, R. V.: Elastic properties of lung in normal men and in patients with chronic pulmonary emphysema. *J. Lab. & Clin. Med.* 40: 674-681, Nov., 1952.

8. Abbott, O. A.; Hopkins, W. A.; Van Fleit, W. E.; and Robinson, J. S.: New approach to pulmonary emphysema. *Thorax.* 8: 116-132, June 1953.

9. Cudkowicz, L.; and Armstrong, J. B.: Bronchial arteries in pulmonary emphysema. *Thorax.* 8: 46-58, Mar. 1953.

10. Syner, J. C., and Christianson, C. S.: Simplified pulmonary function studies, use of waterless basal metabolic apparatus and respirometer. *U. S. Armed Forces M. J.* 5: 1000-1012, July 1954.

11. Comroe, J. H., Jr.: Interpretation of commonly used pulmonary function tests. *Am. J. Med.* 10: 356-374, Mar. 1951.

12. Darling, R. C.; Cournand, A.; and Richards, D. W., Jr.: Studies on intrapulmonary mixture of gases; open circuit method for measuring residual air. *J. Clin. Invest.* 19: 609-618, July 1940.

13. Syner, J. C.: Determination of residual air volume by helium dilution technic. *U. S. Armed Forces M. J.*, 5: 1597-1609, Nov. 1954.

14. Meneely, G. R., and Kaltreider, N. L.: Use of helium for determination of pulmonary capacity. *Proc. Soc. Exper. Biol. & Med.* 46: 266-269, Feb. 1941.

15. Baldwin, E. deF.; Cournand, A.; and Richards, D. W., Jr.: Pulmonary insufficiency physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine* 27: 243-278, Sept. 1948.

16. Syner, J. C.: Unpublished data.

17. Syner, J. C.: Unpublished data.

"BEFORE AND AFTER" ATHEROSCLEROSIS

"Many patients operated upon for aneurysms and occlusive disease are in the later decades of life and have a relatively short life expectancy. Thus, the time from operation to death is an opportunity to investigate certain aspects of lipid metabolism as it relates to atherosclerosis. At operation, the diagnosis of atherosclerosis could be made with certainty and the type and extent of the atheromatous lesions recorded. Subsequently, at necropsy, whether months or years later, the arterial system could be re-examined and the findings compared with those obtained previously. Thus, a series of "before and after" observations would be available against which factors such as the natural history of the disease, metabolic alterations, and effectiveness of drug therapy could be evaluated. To a surgeon, at least, this sort of investigation is more appealing than one in which the diagnosis is based solely upon clinical manifestations, the electrocardiogram, and blood lipids, and in which the same indirect criteria are employed in evaluating results."

—OSCAR CREECH, Jr., M. D.
in *American Heart Journal*
p. 642, Nov. 1957

DISSEMINATED COCCIDIOIDOMYCOSIS TREATED WITH AMPHOTERICIN B

ROBERT C. HUNTER, Jr., *Colonel, MC, USA*
EDWARD S. MONGAN, *M. D.*

SINCE amphotericin B became available to us more than a year ago, we have had under observation, at this hospital, nine patients with disseminated coccidioidomycosis. Five were eliminated from the study; two because they had already undergone a clinical and serologic remission, one because he was improving rapidly when the diagnosis was established, one because he had only serologic evidence of dissemination, and one because he had far-advanced disease and died the day of admission. This report describes the results obtained in the treatment of the remaining four patients with amphotericin B.

AMPHOTERICIN B

Amphotericin B is an antibiotic derived from a species of Streptomyces found in a soil sample from the Orinoco River basin in Venezuela. In vitro, it has been shown to have antifungal properties for a wide variety of organisms, including *Coccidioides immitis*. In vivo, it has had an ameliorating effect on mice experimentally infected with *C. immitis*. In neither animals nor humans was there significant toxicity when the drug was given orally, possibly because of its poor absorption from the gastrointestinal tract.

The LD_{50} for intravenous administration in mice was 8 mg per kg. All of the mice that died did so within nine minutes of the infusion with symptoms of ataxia, spasms, and terminal collapse.[1] Littman, Horowitz, and Swadey[2] described one patient who received 28 mg intravenously in 40 minutes. He had convulsions and cardiac standstill, but recovered. Anorexia, nausea, vomiting, chills, and fever have occurred commonly during, and shortly after, intravenous administration. Such reactions may have been minimized by use of salicylates and antihistamines. On prolonged intravenous administration there was a tendency for the blood urea nitrogen to increase, but this has subsided with temporary interruption of therapy.

From William Beaumont Army Hospital, El Paso, Tex.

The poor absorption of amphotericin B given by mouth has led to preference for the intravenous route of administration. The toxicity has necessitated slow infusion and limited dosage. It is currently recommended that the water-soluble salt be dissolved in sterile 5 per cent dextrose in water to a concentration of 1 mg per 10 ml. The solution should be infused slowly intravenously over a period of six hours or more to a maximum dose of 1 mg per kg daily.[1] Littman, Horowitz, and Swadey[2] suggested a maximum dose of 1.6 mg per kg, and believed that infusion on alternate days reduced the chances of nitrogen retention.

Lehan and associates[3] stated that in several instances when administered intravenously, the amphotericin B infiltrated into surrounding subcutaneous tissue. Mild discomfort and redness at the site resulted, but the complication was not serious. Littman, Horowitz, and Swadey repeatedly injected amphotericin B into a knee severely involved with coccidioidomycosis. The drug was well tolerated and appeared to benefit the knee.

TREATMENT OF COCCIDIOIDOMYCOSIS

The acute pulmonary form of coccidioidomycosis is generally a benign, self-limited disease. It offers no serious therapeutic problems although it produces prolonged morbidity at times. Occasionally, a residual granuloma or cavity in the lung requires surgical removal, but the majority of these are asymptomatic and yield to expectant treatment.

The disseminated disease is relatively rare and far more serious, with a mortality of about 50 per cent. In the past 30 months we have treated 14 patients with disseminated coccidioidomycosis with five deaths to date. In one, the course was fulminating and death occurred two weeks after the onset.[4] Others have recovered spontaneously.[5] Still others have followed a chronic and slowly progressive downhill course.

Evaluation of the therapy of disseminated coccidioidomycosis has been difficult because of the irregular course of the disease. The literature has been contradictory on the subject. However, there has been no good evidence that any therapeutic agent in the past has favorably influenced the course of disseminated coccidioidomycosis.[2, 6] To the long list of ineffective agents we have added chloroquine diphosphate. We had two patients who recovered following the use of chloroquine. Our initial enthusiasm was properly curbed when this drug clearly accomplished nothing for the next seven patients with the disseminated disease.

The collection of clinical data on the therapeutic trial of amphotericin B for disseminated coccidioidomycosis has been slow. There has been little upon which to draw conclusions. Klapper, Smith, and Conant[7] and Fiese[8] each reported one case in which apparent benefit resulted from the oral administration

of amphotericin B. Littman, Horowitz, and Swadey[2] reported two cases in which improvement coincided with intravenous amphotericin B. Preliminary reports to the Squibb Institute for Medical Research[1] included four additional cases, two on oral therapy and two on intravenous therapy. The results were encouraging.

CASE REPORTS

Case 1. A 34-year-old Negro was admitted to this hospital on 10 December 1956, complaining of chest pain. About one month earlier he had noted the onset of fever, malaise, easy fatigability, shortness of breath, right-sided pleuritic type pain, cough, and occasional hemoptysis. He had been stationed in El Paso for six months in 1950, and again for nine months prior to admission.

On examination he appeared well developed, well nourished, and in no distress. His height was 70 inches; weight, 215 lb; temperature, 98.0°F; pulse, 80; blood pressure, 120/82 mm Hg. There was slight dullness and decreased breath sounds over the right lung base posteriorly. Roentgenograms of the chest showed scattered nodular densities in the left lung, an infiltration in the right lung base, and right hilar lymphadenopathy.

The white blood cell count was 11,600 per μl, with 26 per cent eosinophils. The hemoglobin 13.5 grams per 100 ml. *C. immitis* was cultured from the sputum. Reaction to the coccidioidin skin test was positive. Complement fixation for coccidioidomycosis was positive in a titer of 1:64.

One month after admission a 3- by 6-cm mass of lymph nodes was noted in the right supraclavicular area. A specimen for biopsy showed a granulomatous reaction with numerous giant cells containing thick-walled spherules and endospores. Culture of the material was positive for *C. immitis*. An abscess appeared at the biopsy site, and culture of the pus was positive for *C. immitis*. A draining sinus persisted in this area for three months, after which it healed spontaneously.

In March 1957 a coccidioidal abscess developed in the middle phalanx of the fourth toe on the patient's left foot. This was incised and drained. The resulting sinus healed about a month later.

During the first two months in the hospital the patient's general condition remained good, but he lost 35 lb in weight. By early June, his infection appeared to be under control. A roentgenogram of his chest was clear and there was no evidence of active lesions. On 6 June therapy with amphotericin B by mouth was initiated, the patient receiving approximately 5 grams daily for 38 days. The drug was well tolerated.

His complement fixation for coccidioidomycosis was 1:16 on 27 June, and 1:8 on 5 July. He was discharged to duty on 7 August.

On follow-up examination on 13 February 1958, he appeared well. Blood cell count and roentgenographic findings of the chest were normal. His complement fixation was 1:4.

Comment: This patient was on the road to recovery when treatment with amphotericin B was started. There was no reason to believe that the drug altered the course of his disease.

Case 2. A 40-year-old Negro was admitted to this hospital on 28 January 1957, complaining of malaise and cough. For the preceding two weeks he had had low-grade fever, night sweats, headache, malaise, and cough productive of small amounts of yellow sputum. He had been stationed in El Paso for two and one-half years.

Examination revealed a somewhat obese man who was not in acute distress. His height was 69 inches, weight, 200 lb; temperature, 99.1°F; pulse, 88; and his blood pressure was 125/75 mm Hg. There were dullness and fine rales over the right lung base posteriorly. There was a single 3-mm granuloma in the skin of the dorsum of the right wrist. A roentgenogram of the chest showed a pneumonitis in the right lung base and right hilar lymphadenopathy.

The white blood cell count was 7,500 per μl, with 14 per cent eosinophils. The hemoglobin was 13.5 grams per 100 ml. Coccidioidin skin tests were negative throughout the course of his disease. *C. immitis* was cultured from his sputum. Complement fixation for coccidioidomycosis was negative.

About one month after admission a hard mass was noted in the right supraclavicular area. It gradually increased in size and became fluctuant. On 5 April it was incised. *C. immitis* was recovered from the pus. Three months after admission the patient had lost about 30 lb in weight, his complement fixation for coccidioidomycosis had become positive in a titer of 1:256, and numerous new granulomata had appeared in the skin. *C. immitis* was identified microscopically and by culture in several of the skin lesions. The granulomas tended to break down leaving indolent ulcers, 1 to 3 cm in diameter, draining bloody purulent material (fig. 1).

Six months after admission the patient's condition stabilized. He regained his normal weight and appeared healthy with the exception of the ulcerations of his skin. His complement fixation had dropped to 1:64. A roentgenogram of the chest showed no change since admission.

In September, nine months after admission amphotericin B was started, 45 mg intravenously ever other day. The patient regularly had chills, fever, and vomiting during and up to 12 hours after administration of the drug. In November, treatment was discontinued for two weeks because of elevation of his blood urea nitrogen. Between 22 September and 18 December he received a total of 1,125 mg of amphotericin B.

While on therapy all of his skin lesions healed, roentgenographic findings of his chest became normal, and his complement fixation

dropped from 1:64 to 1:8. He was discharged to duty, apparently well, on 26 February 1958.

Figure 1 (case 2). Indolent coccidioidal ulcer on the thigh.

Comment. The results in this patient may have represented no more than the natural course of his disease. The distinct improvement in his skin and lungs during the course of therapy, however, was at least suggestive that the drug was beneficial.

Case 3. A 27-year-old Negro was admitted to the hospital on 22 December 1956, complaining of cough. One month earlier he had noted the onset of bilateral chest pain and a cough occasionally productive of yellow sputum. One week before admission a painful swelling appeared on the left side of his neck. He had no fever, but did have a night sweat the evening before admission. He had lost 5 lb in weight. He had been stationed in El Paso for two months.

On examination he did not appear acutely ill. His temperature was 98.6°F; pulse, 120; blood pressure, 112/70 mm Hg; height, 70 inches; weight, 158 lb. There was a tender mass, measuring 3 to 4 cm in diameter, in the left supraclavicular fossa. A roentgenogram of the chest showed a linear infiltration in the left lower lung field, left hilar lymphadenopathy, and a soft nodular density in the left paratracheal region.

The coccidioidin skin test was positive. The white blood cell count was 11,700 per μl with 15 per cent eosinophils. The hemoglobin was

13.5 grams per 100 ml. *C. immitis* was cultured from the sputum. Complement fixation for coccidioidomycosis was positive in a dilution of 1:256. Biopsy of the left supraclavicular mass showed a granulomatous tissue within which were many giant cells containing thick-walled spherules with endospores. Culture of pus from the abscess which appeared at the biopsy site was positive for *C. immitis*.

The patient's initial course was downhill. He had a low-grade fever, appeared moderately toxic, and became bedridden. He lost 33 lb in weight during the first three months in the hospital. Six weeks after admission a tender fluctuant mass appeared over the right fifth rib just lateral to the midclavicular line. It measured 3 to 4 cm in diameter and 1.5 cm in elevation. *C. immitis* was cultured from pus obtained by needle aspiration of this abscess.

On 5 June 1957, intravenous therapy with amphotericin B was started. The initial dose was 15 mg daily for one week, 30 mg daily the second week, then 45 mg daily. On 21 June treatment was interrupted because of an elevated blood urea nitrogen. It was reinstituted on 28 June in doses of 30 to 45 mg every other day until 18 November when it was again stopped when the blood urea nitrogen was found to have increased. He invariably had nausea, vomiting, chills, and fever while treatment was administered. Acetylsalicylic acid and antihistamines were ineffective in controlling these reactions.

The abscess over the left fifth rib did not change in size from the time of its appearance in February until July. On 17, 23, and 29 July, it was drained through a large gage needle, and 20 mg of amphotericin B dissolved in 2.5 ml of water was injected into the cavity through the same needle. There was no evidence of any local irritation to the amphotericin B. The abscess decreased slowly in size and by 16 August had disappeared.

On 18 November the amphotericin, intravenously, was discontinued after a total dose of 2,550 mg over a six-month period. During the course of treatment the patient's general condition gradually improved. His strength and energy returned; the fever, except for that associated with administration of amphotericin, disappeared; he became ambulatory, and gained 15 lb in weight. His complement fixation titer for coccidioidomycosis dropped from 1:256 to 1:64. He was discharged to duty on 13 December.

He was readmitted on 10 February 1958, complaining of pain in his neck and low back. There was straightening of the cervical and lumbar curves and spasm of the strap muscles in the same areas. Motion of the neck was limited. There was tenderness to percussion over the lumbar spine. Several small lymph nodes were palpable in the anterior cervical and inguinal areas. There was a crusted papular lesion, 1 cm in diameter, on the point of the right elbow. Roentgenograms of the lumbar spine showed an osteolytic lesion, 1.5 cm in diameter, in the body of the fourth vertebra.

Microscopic examination of a biopsy sample from the papule on the left elbow revealed characteristic findings of coccidioidomycosis,

including the presence of the organism. The complement fixation for coccidioidomycosis was positive in a titer of 1:32. The lesion in the lumbar spine was presumed to be caused by coccidioidomycosis.

On 25 February amphotericin B, intravenously, was again started. The dose was rapidly increased to 50 mg every other day. The patient had chills and fever with each administration. In late March the drug was stopped for two weeks because of nitrogen retention. By 30 May, he had received an additional 1,890 mg of the drug, and a total of 4,440 mg intravenously. There has been no significant change in his condition on this last course of treatment and he continued to appear well except for the limitation in motion of his neck. His complement fixation had dropped to 1:16 in May.

Comment. This patient was severely ill and bedridden when amphotericin B was started. Improvement was noted coincidentally with the use of the drug. The evidence was suggestive that the drug was beneficial. Particularly notable was the rapid subsidence of the indolent abscess of his rib when injected locally with amphotericin. The appearance of new lesions of the skin and bone in February 1958 indicated continued dissemination in spite of the falling titer on the complement fixation test.

Case 4. A 22-year-old Negro was admitted to the hospital on 15 January 1958. In early December 1957 he had noted the onset of chills, fever, malaise, myalgia, back pain, nonproductive cough, anorexia, and a weight loss of 15 lb. He had been admitted to Biggs Air Force Base dispensary, El Paso, Tex. on 4 January 1958. There he was found to have fever, lymphadenopathy in the inguinal and anterior cervical areas, and a small papule over the right eye. His white blood cell count was 24,000 per μl, with 30 per cent eosinophils. He had been stationed in the El Paso area for 18 months.

Examination showed a thin, acutely and chronically ill man who had lost a total of 25 lb in weight. His height was 68 inches; weight, 135 lb; pulse, 96; respirations, 30 per minute; temperature, 102.1°F; and his blood pressure was 140/87 mm Hg. There were numerous lymph nodes, measuring 2 to 3 cm in diameter in the anterior cervical, femoral, and inguinal areas. The liver was palpated 3 cm below the costal margin, and the spleen at the costal margin. There were scattered granulomatous skin lesions measuring 6 to 8 mm in diameter. There was one larger skin lesion over the right eyebrow, measuring 1.5 cm in diameter and 0.6 cm in elevation (fig. 2). A roentgenogram of the chest showed an infiltration in the right cardiophrenic angle and bilateral hilar lymphadenopathy.

The white blood cell count was 20,550 per μl, with 10 per cent eosinophils. His hemoglobin was 11.8 grams per 100 ml. The coccidioidin skin test remained negative on monthly testing. *C. immitis* was cultured from the lesion above the right eye, from pus aspirated from an anterior cervical lymph node, and repeatedly from the sputum. Biopsy of the skin lesion above the right eye revealed a

granuloma containing numerous thick-walled organisms with endospores. Complement fixation titer for coccidioidomycosis was 1:16.

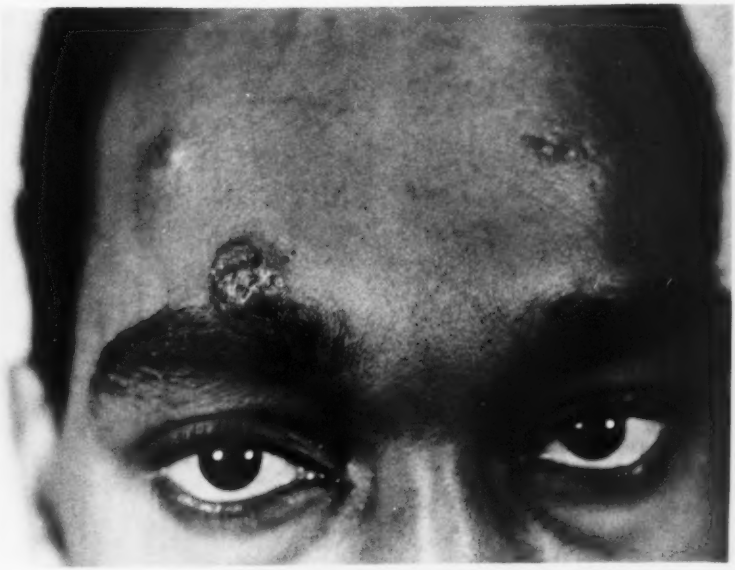

Figure 2 (case 4). Coccidioidal granulomata on the face.

Treatment with amphotericin B, intravenously, was initiated on 24 January. By 30 May, the patient had received a total of 2,970 mg in four months. The dosage eventually was stabilized at 50 mg every other day. The patient routinely had severe febrile reactions on each administration. On two occasions a rise in his blood urea nitrogen necessitated temporary cessation of treatment.

On different occasions, pus was aspirated through a 16-gage needle from six enlarged fluctuant nodes in the neck, groin, and femoral areas, and 25 mg of amphotericin B dissolved in 2.5 ml of water was injected. Four were injected twice. There was no apparent local irritation to this procedure. Although he was receiving intravenous medication at the time, *C. immitis* was cultured from the pus from most of these nodes. All of the locally treated lesions decreased in size and became nonfluctuant over a period of 3 to 6 weeks after injection (figs. 3 and 4), but only one had completely disappeared.

His condition on admission was poor. He had a septic fever with a temperature of 103 to 104°F daily, and little appetite. About one week after admission he began to complain of severe pain in the left upper abdominal quadrant. On examination he had tenderness and rigidity of the abdominal wall in this area. There also was a partial paralytic ileus with considerable abdominal distension. This progressed to generalized abdominal tenderness and moderate ascites. A diagnostic

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abdominal paracentesis was not performed, but the findings and course were thought compatible with coccidioidal peritonitis. The patient's condition appeared to be terminal at this time and he was carried on the seriously ill list. He had anemia severe enough to require four blood transfusions during his second month in the hospital.

Figure 3 (case 4). Coccidioidal abscesses in subinguinal lymph nodes shortly after they were first injected with amphotericin B.

In March, gradual and persistent improvement began. His ascites diminished, his appetite improved, the lymphadenopathy decreased, the hemoglobin stabilized at 10 grams per 100 ml and the skin lesions decreased in size. His fever continued, but the daily peaks were lower, 100 to 101°F. His strength returned and he was able to ambulate partially. No new lesions of the skin, lymph node, or bone appeared after amphotericin B was started on 24 January. The patient was far from well, but by May was much improved. In spite of the clinical improvement, his complement fixation rose from 1:16 on admission to 1:128 five months later.

Comment. This patient was moribund when treatment with amphotericin B was started. We were fearful that he would be unable to tolerate the toxic reactions to the drug. At the same time, the prognosis in a Negro patient with disseminated coccidioidomycosis of this severity is so unfavorable that it did not appear

reasonable to withhold treatment. His improvement was not dramatic but it was impressive. Interestingly, his complement fixation titer rose as he improved clinically.

Figure 4 (case 4). Same area shown in figure 3, two months after second injection of amphotericin B into abscess cavities.

DISCUSSION

The cases presented differed in severity but were otherwise surprisingly similar. The following features were common to all four: Negro race, pulmonary symptoms at onset, fever, pulmonary infiltrations with hilar lymphadenopathy, early dissemination, marked weight loss, eosinophilia, sputum culture positive for *C. immitis,* complement fixation for coccidioidomycosis positive in dilution of 1:64 or more, peripheral lymph node involvement, abscess formation in peripheral nodes, and positive culture for *C. immitis* from the abscesses. Three patients had granulomata of the skin, two had a positive reaction to the coccidioidin skin test, two had bone lesions. One had anemia.

Our use of amphotericin B by mouth was limited to a short course of 38 days given to the first patient. Although the patient recovered, we were unable to draw any conclusions on this mode of administration.

The three patients who received amphotericin B intravenously reacted predictably with anorexia, nausea, chills, and fever on every administration. The reactions tended to decrease slightly in severity with continued medication, but remained severe after months of treatment. Salicylates and antihistamines were ineffective in our hands in altering the reactions. All three patients had an elevated blood urea nitrogen one or more times during treatment. This subsided on each occasion upon interrupting therapy for one or two weeks. Because of the unfavorable reactions, we were unable to exceed a dose of 50 mg (0.7 to 0.9 mg per kg), given over a six-hour period, every other day. This particular dosage may have been prompted to some extent by the packaging of the amphotericin B in 50-mg vials. Littman, Horowitz, and Swadey[2] independently arrived at the same conclusion as to frequency of medication, but were successful in giving larger doses. Our patients suggested that the infusions be started immediately after supper so as not to interfere with food intake. This was a useful consideration in treating a disease in which weight loss, malnutrition, and poor body resistance were important factors.

The results of treatment in a disease as unpredictable as disseminated coccidioidomycosis must be accepted with caution. Our three patients improved while on intravenous amphotericin B therapy. It appeared likely that the favorable course of the disease was in part brought about by the drug. The response, if any, was slow. We were still able to culture *C. immitis* from a variety of areas in these patients after they had been treated intravenously with amphotericin B for months. We were unable to avoid speculating as to what might have been accomplished had we been able safely to give 10 or 100 times as much drug intravenously.

We injected amphotericin B into 7 coccidioidal abscesses, 1 in bone and 6 in lymph nodes. Two were injected once, 4 twice, and 1 three times, with about a week between injections. Positive cultures were obtained from nearly all of the abscesses, although the patients were receiving amphotericin B intravenously at the time. The dose was 20 to 25 mg dissolved in 2.5 ml of water. There were no untoward local or systemic reactions to to the injections. All of the abscesses had been present for several months, and were either stationary or increasing in size when local treatment was started. The response was uniformly favorable. Two lesions healed completely in four to six weeks. The other five lesions decreased in size and became nonfluctuant in three to six weeks, but a residual firm mass remained. There seemed to be little doubt that the injection of amphotericin B

directly into coccidioidal lesions was effective and useful. We believed that the relatively high concentration obtained in the abscess cavities explained the excellent response.

Smith[9] believed that the abdominal pain, partial ileus, and ascites in the fourth patient were manifestations of coccidioidal peritonitis. Retrospectively, diagnostic paracentesis and intraperitoneal injection of amphotericin B would have been desirable and possibly beneficial. At the time this report was written, the patient had improved to the extent that this measure was no longer under consideration.

The results obtained with amphotericin B intravenously indicated that it possibly was useful in treating disseminated coccidioidomycosis. The results obtained with direct injection of coccidioidal abscesses were more impressive. Amphotericin B in all probability represents the first real advance in the treatment of disseminated coccidioidomycosis, but further clinical testing will be essential. A similar agent with equal effectiveness but less toxicity could prove to be the answer to the therapy of coccidioidomycosis.

SUMMARY

Four patients with disseminated coccidioidomycosis were treated with amphotericin B, one orally and three intravenously. The usefulness of the oral drug was not determined. The three patients on the intravenous preparation were treated for periods of 3 to 12 months. All improved while on therapy. Amphotericin B administered intravenously regularly caused chills, fever, anorexia, and nausea, during and shortly after each infusion. Salicylates and antihistamines did not alter these reactions. Azotemia occurred one or more times in each patient on intravenous therapy, but subsided upon interrupting treatment for one or two weeks. The unfavorable reactions were minimized by limiting the dose to 50 mg, given every other day immediately after supper. The water-soluble salt was dissolved in 5 per cent dextrose water to a concentration of 1 mg per 10 ml and infused slowly. Six hours or more were taken for each infusion.

Seven coccidioidal abscesses in two of the patients were injected directly with 20 to 25 mg of amphotericin B dissolved in 2.5 ml of water. Two were injected once, four twice, and one three times, the injections being about one week apart. The abscesses had been present for several months and were either stationary or increasing in size when injected. The response was uniformly favorable and fluctuation disappeared in three to six weeks.

Amphotericin B appeared to be an effective agent for the treatment of disseminated coccidioidomycosis. Its toxicity has limited the dosage, which, in turn, may have limited its effectiveness.

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REFERENCES

1. Summary of Information for Clinical Investigators; Fungizone. The Squibb Institute for Medical Research, March 6, 1957.

2. Littman, M. L.; Horowitz, P. L.; and Swadey, J. G.: Coccidioidomycosis and its treatment with amphotericin B. *Am. J. Med.* 24: 568-592, Apr. 1958.

3. Lehan, P. H.; Yates, J. L.; Brasher, C. A.; Larsh, H. W.; and Furcolow, M. L.: Experiences with therapy of 60 cases of deep mycotic infections. *Dis. Chest* 32: 597-614, Dec. 1957.

4. Mongan, E. S.: Acute disseminated coccidioidomycosis. *Am. J. Med.* 24: 820-822, May 1958.

5. Ward, J. R., and Hunter, R. C.: Disseminated coccidioidomycosis demonstrated by needle biopsy of the liver. *Ann. Int. Med.* 48: 157-163, Jan. 1958.

6. Procknow, J. J., and Loosli, C. G.: Treatment of deep mycoses. *A. M. A. Arch. Int. Med.* 101: 765-802, Apr. 1958.

7. Klapper, M. S.; Smith, D. T.; and Conant, N. F.: Disseminated coccidioidomycosis apparently cured with amphotericin B. *J. A. M. A.* 167: 463-466, May 24, 1958.

8. Fiese, M. J.: Treatment of disseminated coccidioidomycosis with amphotericin B; report of case. *California Med.* 86: 119-120, Feb. 1957.

9. Smith, C. E.: Personal communication.

MODERN SCIENCE AND CIVILIZATION

"As an instrument, science can achieve either good or ill. That will depend upon the minds and spirits of those who use the instrument. Our natural and acquired capacity for extravagance, skillfully played upon by the sensationalists of the fleeting day, can too easily lead us to believe that the need for more scientists is such that all other higher studies should be subordinate; that the study of physical nature is the only thing that greatly matters; that if knowledge comes, wisdom will not linger. Believing as I do that science and wisdom have no necessary connection, and that scientific study and achievement are not ends but means, I am driven to the conclusion that what the scientists do or will do will put into our hands discoveries which can be the means of destruction or of a new and complicated form of technological slavery, but which, wisely used, can be the means of human salvation. The answer will depend upon our character, our broad intelligence, and our wise and understanding judgment."

—R. G. MENZIES,
in *The Medical Journal of Australia*
p. 516, Apr. 19, 1958

Clinicopathologic Conference

Walter Reed Army Hospital, Washington, D. C.*

WEAKNESS OF ONE YEAR'S DURATION

Summary of Clinical History. A 59-year-old retired officer was admitted to this hospital for the second time on 22 July 1957. He apparently was well until January 1955 when an annual physical examination revealed albuminuria. He was asymptomatic and refused hospitalization for diagnostic study. In June 1955, he noted ankle swelling and decrease in exercise tolerance. The following September he was retired from the Army. During the following year, he noticed increased fatigability and numbness and paresthesia in his left knee. In October 1956, he was seen in the out-patient clinic where he was found to have hypertension. Urinalysis revealed a specific gravity of 1.020 and albuminuria ranging from 1 plus to 4 plus. The phenolsulfonphthalein excretion was 9 per cent in 15 minutes and 34 per cent in two hours. There was bilateral pitting ankle edema. Because of this edema, the patient was given digitalis and a course of phenobarbital and Serpasil (brand of reserpine), 0.25 mg three times a day. Laboratory studies performed at this time revealed a blood urea nitrogen of 17.7 mg per 100 ml and a total serum protein of 5.4 grams (albumin, 2.3 grams, globulin, 3.1 grams) per 100 ml. An intravenous pyelogram was interpreted as normal.

First Hospitalization. On 5 December the patient was admitted to the hospital because of weakness. Blood pressure was 180/110 mm Hg. Fundi showed Grade I changes. The heart was slightly enlarged. The liver edge was 1 to 2 cm below the right costal margin at the midclavicular line. There was a 2 plus

*Maj. Gen. Leonard D. Heaton, MC, USA, Commanding General. From the Laboratory Service, Col. Roland S. Aronson, MC, USA, Chief.

bilateral pitting ankle edema. Cholesterol varied between 280 and 330 mg per 100 ml. Congo red test showed 46 per cent retention. The patient spilled between 5 and 8 grams of protein each 24 hours. Addis count showed 1,330,000 casts, 1,500,000 red blood cells, and 1,000,000 white blood cells. His hemoglobin dropped from 14.5 grams to 12.5 grams per 100 ml. On 4 January 1957, his total serum protein was 5.4 grams (albumin, 1.9 grams, globulin 3.5 grams) per 100 ml; blood urea nitrogen, 41 mg per 100 ml; creatinine, 2.2 mg per 100 ml; and uric acid, 8 mg per 100 ml. A retrograde pyelogram was normal. The patient was maintained on a low-sodium diet, and lost 20 pounds. On 17 January, he was discharged from the hospital and advised to follow a low-sodium, high-protein diet. At home he slowly became more fatigued, and he noticed increasing dyspnea and anorexia. Three months after discharge he began having constant boring pains and paresthesias from his knees down. These symptoms were partially relieved by leg elevation.

SECOND HOSPITALIZATION

On 22 July 1957, the patient was readmitted to the hospital because of severe nausea and vomiting and increased fatigability. For the past 25 years he had been told that his blood pressure was elevated and on several annual physical examinations he had been recalled for rechecks. For two years prior to admission he had had nocturia five times per night. His past history otherwise was noncontributory.

The patient's mother, two brothers, and one sister died of tuberculosis. The father died at the age of 70 from a cerebrovascular accident. Six other siblings ranging in age from 49 to 74 years were living and well.

Physical Examination. The patient was a well-developed, well-nourished man who appeared chronically ill. There was some puffiness about the face. He was slightly tremulous and obviously depressed. His pupils reacted weakly to light and accommodation but were equal and regular. Funduscopic examination showed small areas of exudate and some narrowing of the arterioles, but no A-V nicking. The tongue was of normal size. The lungs were clear to percussion and auscultation. There was no cardiomegaly; the heart sounds were of good quality with A_2 equal to P_2. A Grade I blowing early systolic murmur was heard at the apex. The abdomen was normal, and the liver was not palpable. There was 1 plus pitting edema of both lower extremities. Prominent popliteal and good pedal pulses were present. There was slight pallor on elevation of both feet. Neurological examination revealed a slight intension tremor, which was greatest in the left arm; generalized hyporeflexia; and generalized weakness.

Laboratory Studies. On 23 July the white blood cells numbered 13,000 per μl, with a normal differential count. Hemoglobin was 8.3 grams per 100 ml; hematocrit was 25.5 ml per 100 ml. Corrected sedimentation rate was 22 mm per hour. Slight anisocytosis and hyperchromasia of the red cells were noted. Urinalyses on several occasions revealed specific gravity ranging from 1.010 to 1.014 and a persistent 4-plus albuminuria. The total volume of urine was markedly decreased. A serum-electrophoretic study showed a total protein of 4.7 grams per 100 ml, with 34 per cent albumin, 10 per cent alpha$_1$ globulin, 22 per cent alpha$_2$ globulin, 20 per cent beta globulin, and 14 per cent gamma globulin. A serologic test for syphilis was negative. Microscopic examination of the urine revealed from 6 to 10 granular casts per low-power field and some white blood cells. Electrolyte studies performed were normal; serum uric acid was 8.4 mg per 100 ml.

On 26 July, an Addis count showed 278,000 white blood cells, 224,000 red blood cells, and 150,000 casts. The total volume of urine was 900 ml. A phenolsulfonphthalein test showed 1 per cent excretion in 15 minutes and a total of 6 per cent excreted in 2 hours. Urine culture grew alpha streptococci, sensitive to various antibiotics.

On 29 July the blood urea nitrogen was 100 mg per 100 ml; sodium, 122 mEq per liter; potassium, 6.7 mEq per liter; carbon dioxide combining power, 18.2 mEq per liter; and chlorides, 89 mEq per liter. On 7 August the blood urea nitrogen rose to 138 mg per 100 ml.

An electrocardiogram taken on admission revealed multiple premature ventricular contractions from multiple foci, as well as runs of apparent ventricular tachycardia. The basic tracing remained within normal limits. On 10 August, an electrocardiogram showed a complete right bundle-branch block.

Roentgenograms taken on this admission showed the heart enlarged in its anteroposterior and transverse diameters. There was a prominent, dilated, and tortuous thoracic aorta with some increased radiolucency of the lung fields, suggestive of emphysema.

Course in Hospital. The patient remained afebrile throughout his hospitalization. His weight on admission was 164 pounds. On 10 August he weighed 189 pounds. The patient's complaints centered around the swelling of his legs, tenderness of the skin over the feet and ankles, weakness, and shortness of breath. He was treated with Thorazine (brand of chlorpromazine hydrochloride), sodium chloride by mouth, testosterone, 25 mg intramuscularly three times per week, and a 25-gram protein diet. His blood pressure remained stable at 170-175/90 mm Hg. His urinary output declined slowly. By 4 August

he was excreting 400 to 500 ml of urine each 24 hours. This gradually declined until 10 August when his total output in 24 hours was only 45 ml. His blood urea nitrogen and serum potassium steadily climbed. The patient remained mentally clear until his death. During the hospitalization, several units of blood were given to combat the anemia. On five successive days 25 grams of salt-poor albumin were given without affecting the urinary output. The fluid intake was kept to 1,000 ml above the urinary output. On 7 August, 40 units corticotropin, intramuscularly every 12 hours, was started without improvement. The edema persisted in spite of fluid restriction. After several days of nothing by mouth and intravenous fluids, the nausea disappeared. On 11 August the patient began to complain of shortness of breath, and physical examination revealed a gallop rhythm. He was placed in an oxygen tent and given an aminophylline suppository. Soon thereafter he died quietly.

DISCUSSION

Doctor Lynn:* This 59-year-old retired officer apparently was well through his entire Army career except for an elevated blood pressure on several occasions for the past 25 years. These elevations apparently were transitory or labile. The first indication of any renal abnormality was in January 1955, when albuminuria was discovered. In June 1955, he noted some ankle swelling and decrease in exercise tolerance. Between June 1955 and October 1956, he noted a progressive increase in fatigability and numbness and paresthesia around the left knee. At this time, a check-up revealed hypertension, albuminuria, and a decreased phenolsulfonphthalein excretion. Abnormalities, such as a low serum protein with a slight reversal of the albumin-globulin ratio, also were found by laboratory studies. An intravenous pyelogram and the blood urea nitrogen were reported as normal. The patient had bilateral pitting edema. He was considered to have congestive heart failure, and was placed on an antihypertensive regimen along with digitalis.

He was hospitalized from 5 December 1956 until 17 January 1957, because of progressive weakness. At this time he demonstrated a blood pressure of 180/100 mm Hg, ocular fundi that were Grade I, slight cardiomegaly, hepatomegaly, 2-plus bilateral ankle edema, a fairly marked proteinuria, an abnormal Addis count, and a progressive anemia. It also was found that his A/G ratio was reversed and that the serum albumin had dropped to 1.9 grams per 100 ml. Blood urea nitrogen had become elevated to 41 mg per 100 ml. At this time the serum uric acid also was found to be elevated to 8.4 mg per 100 ml, probably on the basis of azotemia. On treatment with the low-sodium diet, he again improved.

The inital question in this case is: Did the patient's mild labile hypertension over the past 25 years play a dominant role in his final

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*Col. Doss O. Lynn, MC, USA, Chief, General Medicine Service.

illness? Inasmuch as a nephrotic syndrome developed and the patient died in renal insufficiency, I do not believe that his hypertension was the etiologic factor.

Because he died in progressive renal failure with a nephrotic syndrome, we should discuss some of the factors producing renal failure in an attempt to make a diagnosis. Diseases producing acute renal failure are usually much easier to diagnose than those causing a chronic progression. Of the many types of chronic kidney disease, the tendency to progress toward a general failure of renal function is present, regardless of the nature of the primary kidney involvement.

One of the ways to think of the diagnostic possibilities is to divide the kidney lesions in an anatomic sense, as outlined by Harvey and Bordley.[1] One type may affect the kidney diffusely and the other may cause localized or circumscribed areas of pathologic change. Certain differences in these anatomic types can be seen in a high percentage of cases. For instance, in a localized condition such as congenital polycystic disease, infarction due to small emboli, tuberculosis, or even chronic pyelonephritis, there may be slowly advancing renal failure and severe impairment of renal function without any symptoms of uremia. An elevated blood urea nitrogen is present and the kidneys are unable to excrete phenolsulfonphthalein dye. This is particularly true if severe hypertension of the malignant type does not develop.

In contrast to diffuse renal disease, such as chronic glomerulonephritis, lupus erythematosus, syphilis, myeloma, amyloidosis, or intercapillary glomerulosclerosis, there are usually severe symptoms of uremia with nausea, vomiting, headache, and so on. Also, in the diffuse type of disease there is usually an increase in urinary sediment, especially in casts and red blood cells.

We also have to consider a few miscellaneous conditions that might cause chronic renal failure, such as vitamin D intoxication, alkaline therapy for peptic ulcer, hyperparathyroidism, medullary congenital cysts with salt-losing effects simulating Addison's disease, sarcoidosis, gout, eosinophilic granuloma, and obstruction of the renal vein.

There are some conditions causing renal failure that may be accompanied by a normal blood pressure if there was no pre-existing hypertension. These include subacute bacterial endocarditis, amyloid disease, myeloma of the kidney, lupus erythematosus, and renal tuberculosis. Periarteritis that involves renal vessels is almost always accompanied by hypertension.

In today's case, it is most difficult to say that this patient did not have a combination of congestive heart failure with terminal arrhythmia and chronic renal failure. Since I believe that this patient had both cardiac and renal involvement, it appears that he had some form of generalized systemic disorder. Of disorders that will give this picture, we should limit consideration to those that are likely to be associated with the nephrotic syndrome. On this basis I believe we can eliminate hypertensive cardiovascular disease with arteriosclerotic type ne-

phritis, since this does not produce nephrosis. On the same basis, we can eliminate periarteritis nodosa because he did not have the severe hypertensive changes which one would expect with this degree of kidney involvement. Also, chronic glomerulonephritis would not be as likely to produce the cardiac manifestations. It would likewise eliminate drug intoxication, syphilitic nephrosis, and intercapillary glomerulosclerosis of the Kimmelstiel-Wilson type, because of lack of evidence of such. There is no other evidence of a myeloma, although the abnormal Bence Jones protein may not be found in renal myeloma. It is more difficult to eliminate lupus erythematosus as a cause of this disease and, therefore, this will have to be strongly considered. There are certain factors, however, against lupus. It would be most unusual in a man of this age, as this disease is rare after 45 and is predominantly seen in females. The course would be an atypical one without febrile episodes, leukopenia, and without other system involvement such as the skin or pleura. Therefore, lupus erythematosus is not my first choice.

This patient probably had myocardial involvement or muscle disease, as manifested by signs of congestive heart failure with apparent early response to digitalis, rest, and diuretics. Terminally, he had a gallop rhythm, indicating myocardial failure. Arrhythmias, however, were not mentioned; if present they would have been another indication of myocardial involvement.

The disease that would best explain this patient's illness and clinical course is primary amyloidosis. There is no evident chronic infection or other obvious cause for secondary amyloidosis. In primary amylodosis the heart and arterial vessel wall may show involvement in addition to the kidney. This disease, producing so-called amyloid nephrosis, is consistent with this patient's clinical course and laboratory findings.

Clinical diagnosis:
Primary amyloidosis of the heart and kidneys

PATHOLOGIC FINDINGS

Doctor Kawas:* The fact that during life this patient had a renal biopsy which proved the diagnosis of amyloidosis was excluded from the clinical abstract. At autopsy, the body was that of a well-developed, fairly well-nourished man, appearing his stated age. The findings of greatest interest were in the kidneys, spleen, and adrenals.

The right kidney weighed 300 grams. The left kidney weighed 290 grams and presented an unusually pale parenchyma which was firm and rubbery in consistency. The capsules of both kidneys stripped with ease, revealing a coarsely granular surface. On section, the corticomedullary differentiation was preserved but not sharply demarcated (fig. 1). Microscopic examination revealed all glomeruli to be abnormal, as a result of the deposition of a pink-staining, homogeneous substance

*Capt. Elias E. Kawas, MC, USA, Resident in Pathology.

throughout the tufts of the glomeruli (fig. 2). This pink-staining substance also was noted in the wall of the blood vessels and some of the tubular basement membranes. There was an increase in interstitial fibrosis throughout both kidneys with corresponding decrease in number of tubules. Special stains were strongly positive for amyloid.

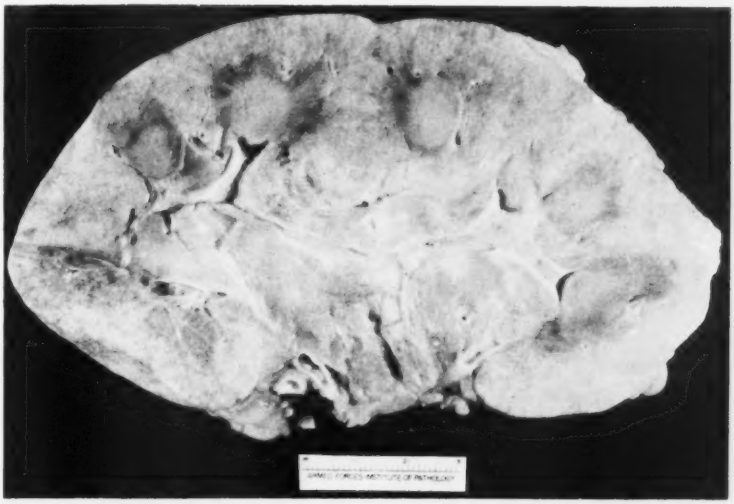

Figure 1. Kidney, cut surface. Note the size and pallor of the organ, the widened cortex, and the ill-defined corticomedullary markings.

The spleen weighed 245 grams. The capsule was smooth and glistening. The cut surface presented a firm and rubbery, translucent, red parenchyma which in no way resembled the normal splenic parenchyma (fig. 3). The Malpighian corpuscles were not discernible. Microscopically, the spleen revealed diffuse deposits of homogeneous, pink-staining, amorphous material, which, similar to the kidneys, was positive for amyloid (fig. 4). These deposits were intercellular and ran along the sinusoids of the spleen.

The adrenals weighed 41 grams combined. This is over three times the normal weight. They presented a granular and unusually friable tissue in which the corticomedullary differentiation was completely lacking. Microscopic examination revealed diffuse deposits of amyloid and only small cords of atrophic adrenal cortical tissue still present. Small deposits of amyloid were also present in the walls of the small arteries of the liver, pancreas, and bone marrow.

The heart weighed 690 grams and was concentrically hypertrophied. It presented a severe degree of atherosclerosis with marked narrowing of the lumina of the larger arteries; however, no occlusions were present. The myocardium showed multiple foci of fibrosis in the posterior

wall of the left ventricle. Microscopically, no evidence of amyloid deposits was noted within the heart. Examination of the tongue and gastrointestinal tract was similarly negative for amyloid. Careful exam-

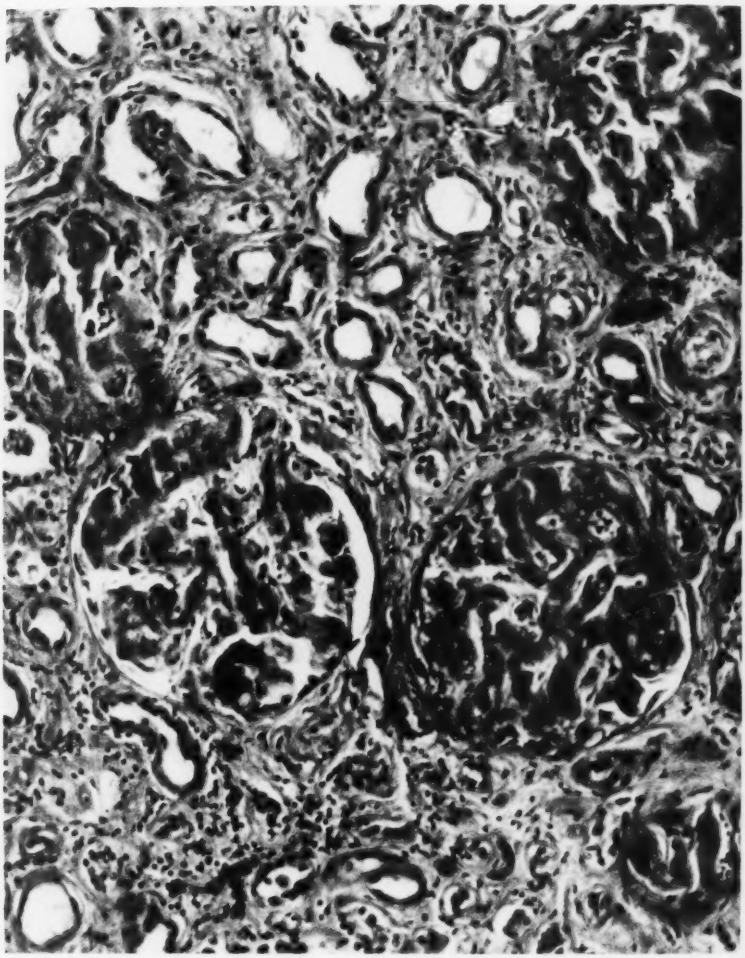

Figure 2. Kidney, photomicrograph. Note obstruction of glomerular loops by amyloid and the severe degree of tubular degeneration and atrophy. (× 110)

ination of the bone marrow for evidence of multiple myeloma was unrevealing. The distribution of amyloid in this case is that of a secondary amyloidosis; however, there was no pathologic condition which might have elicited this response and which could explain the derangement of the protein metabolism with the resultant amyloid deposits.

Figure 3. Spleen, cut surface. Note the absence of Malpighian corpuscles, the pallor of the organ, and the waxy sheen of the cut surface.

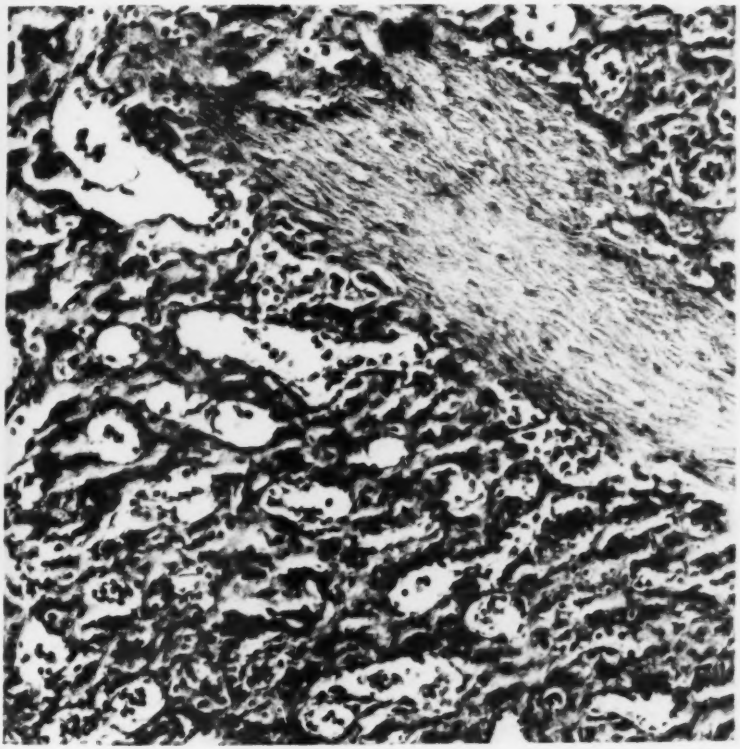

Figure 4. Spleen, photomicrograph. Note the massive deposits of amyloid in the splenic cords completely replacing the lymphoid elements. (× 110)

This is one of many cases which does not fit into the old classification of primary and secondary amyloidosis, a division which in the light of modern concepts appears obsolete.

Pathologic diagnoses:

1. Primary amyloidosis, involving kidneys, spleen, adrenals, liver, pancreas, and bone marrow
2. Arteriosclerosis and hypertensive cardiovascular disease

COMMENTS

Doctor Sprinz:* The concept of amyloidosis as a systemic disease was developed by Rudolph Virchow. He established the distribution of organ lesions and the histopathology, and considered the disease to be a derangement of cellular metabolism. The various manifestations and organ involvements in amyloidosis had been noted for centuries by various observers, but it remained for Virchow's keen insight and astute power of observation to bring them under a common denominator. He had studied some of the rather characteristic color reactions which are elicited by Lugol's solution and sulfuric acid on amyloid, and under the mistaken belief that he was dealing with a starch or cellulose-like compound he gave the disease its name, amyloidosis, under which it is still known today. Virchow announced his discovery to the general medical public in one of a series of 20 lectures which he delivered in the spring of 1858 at the University of Berlin. The lectures created a sensation in their day and were published in the same year in book form. This book, *Cellular Pathology*,[2] has remained a classic. It went through many editions and was translated into every civilized language. It is one of the most influential books in modern medicine.

It is a peculiar fact that very little has been added to our knowledge of amyloidosis in the past 100 years. We know now that it is a proteinaceous substance, the exact composition of which has yet to be determined. We are still in the dark about the mechanism of its deposition and its occasional removal. In its so-called secondary form, it is associated with and is a complication of long-standing suppurative infections, such as chronic osteomyelitis and tuberculosis. It may appear within the matter of a few months, but more frequently it occurs after a period of years following the establishment of a chronic infection or debilitating condition. Its progress is variable. Since the advent of modern therapy, which has practically eliminated such prolonged suppurative diseases, secondary amyloidosis has become a rarity. Animal experimentation has thrown little light on its pathogenesis. We know that marked species differences exist in the ease in which amyloidosis can be produced. In susceptible animals, amyloidosis follows flooding the body with foreign protein. This has given rise to the hypothesis that an *in vivo* antibody-antigen reaction is involved, with precipitation

*Lt. Col. Helmuth Sprinz, MC, USA, Chief, Pathology Section, Laboratory Service.

of amyloid at the reaction sites. Different chemical composition of antigen and antibody could then account for the observed chemical differences in the composition of amyloid. Preferred sites of amyloid deposition are cells of the reticuloendothelial system, a fact which may be associated with the hyperglobulinemia not infrequently observed in amyloidosis.

When we attempt to correlate the autopsy findings with the clinical evolution of the disease in our patient, we note that the long-standing, mild to moderate hypertension is reflected in the moderately severe, concentric hypertrophy of the heart which characteristically was only slightly enlarged on roentgenographic examination. In addition, the patient had a severe degree of coronary sclerosis with myocardial scarring. His arteriosclerotic hypertensive heart disease undoubtedly was aggravated by the progressive renal failure incident to the amyloidosis to which he eventually succumbed. As previously stated, however, the heart was free of amyloid deposits. The albuminuria first noted in January 1955 was most likely the initial manifestation of renal involvement by amyloid. Proteinuria is an almost invariable accompaniment of renal amyloidosis, although, for reasons yet unknown, there is no correlation between the amount of amyloid deposited in the kidney and the degree of albuminuria. Unfortunately, in our case, the urinary proteins were not studied electrophoretically. It is said that of all conditions leading to proteinuria, renal amyloidosis is associated with the highest admixture of globulin. While in lipoid nephrosis, for instance, the albumin-globulin ratio of urinary protein is about 10 to 1, in renal amyloidosis it is often less than 5 to 1, and may even approach a ratio of 2 to 1. The pitting ankle edema which was first noted in June 1955 was probably due to a combination of low plasma albumin and mild heart failure. The Addis count performed in December 1956 reflects the predominantly glomerular involvement in renal amyloidosis. As more and more glomerular tufts became obstructed by amyloid deposits, the specific gravity of the urine dropped from 1.020 to 1.010. The progressive atrophy of nephrons accounts for the unremitting renal failure. At autopsy, every glomerulus was severely affected, and not a single normal nephron had remained. The amyloid deposits in the remainder of the organs apparently had little functional significance. Even the marked involvement of the adrenals had not led to any signs or symptoms of Addison's disease.

REFERENCES

1. Harvey, A. McG., and Bordley, J., III: *Differential Diagnosis.* W. B. Saunders Company, Philadelphia, Pa., 1955. pp. 157-160.

2. Virchow, R.: *Cellular Pathology.* 7th American edition. Robert M. DeWitt, New York, N. Y. pp. 409-427.

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CASE REPORTS

Collision Tumor

ROBERT C. THOMAS, *Lieutenant, MC, USN*
ALBERT CANNON, *Lieutenant Commander, MC, USN*

IN a collision tumor a sarcoma invades a carcinoma, or vice versa. There are numerous reports in the literature concerning various types of "carcinosarcomas",[1-7] but few have been generally accepted as true carcinosarcomas. A case of collision tumor in which both the carcinomatous and the sarcomatous elements have metastasized, and which is thought to be a true case of dual malignancies developing in juxtaposition, is presented.

CASE REPORT

A 69-year-old retired chief petty officer was admitted to the U. S. Naval Hospital, Annapolis, Md., complaining of difficulty in swallowing solid food. He had been well until four weeks prior to admission when he noticed the onset of a sore throat and pain in the left side of his neck. Dysphagia for solid food developed thereafter. A large, fungating, polypoid lesion was found on the posterior aspect of his tongue to the left of the midline. A biopsy specimen was reported as demonstrating anaplastic squamous-cell carcinoma, and the patient was transferred to the U. S. Naval Hospital, Bethesda, Md., for treatment.

Physical examination on admission to this hospital disclosed a mushroomlike lesion, measuring 2 by 3 by 5 cm, attached to the posterior part of the tongue to the left of midline by a short, relatively narrow pedicle 1.5 cm in diameter, and partially occluding the oropharynx. The mass was friable, bleeding easily with trauma. Induration extended laterally into the floor of the mouth, medially to the midline of the tongue, and inferiorly into the neck to a point just superior to the hyoid bone. No discrete nodes were palpated. Advanced peripheral arterial changes in both legs, more marked on the right, were evident. Pulses were absent below the femorals bilaterally.

Routine laboratory studies, including blood cell counts, urinalysis, and roentgenograms of the chest, mandible, and skull were within normal limits.

The tumor board recommended that the lesion be removed surgically. This was accomplished on 27 November 1957 by a left hemiglossectomy and with radical neck dissection. A tracheotomy was performed, and a Levin tube placed for feeding.

From U. S. Naval Hospital, Bethesda, Md.

Postoperatively the patient showed moderate confusion, which was thought to be a result of arteriosclerosis. This quickly cleared. The operative sites healed well. The patient's progress was rapid and he was soon taking full oral feedings. Unfortunately, ten days postoperatively, the patient developed further ischemic changes in his right leg which progressed to frank dry gangrene in spite of treatment by peridural block and anticoagulants. An above-knee amputation was necessary, from which recovery was uneventful.

Pathologic Findings. After review of multiple sections of the surgical specimen (figs. 1-6), the diagnosis of a true collision tumor was made. The epithelial part of the tumor (figs. 3 and 6) was unquestionably a squamous-cell carcinoma showing both deep invasion of the tongue and metastases to nodes.

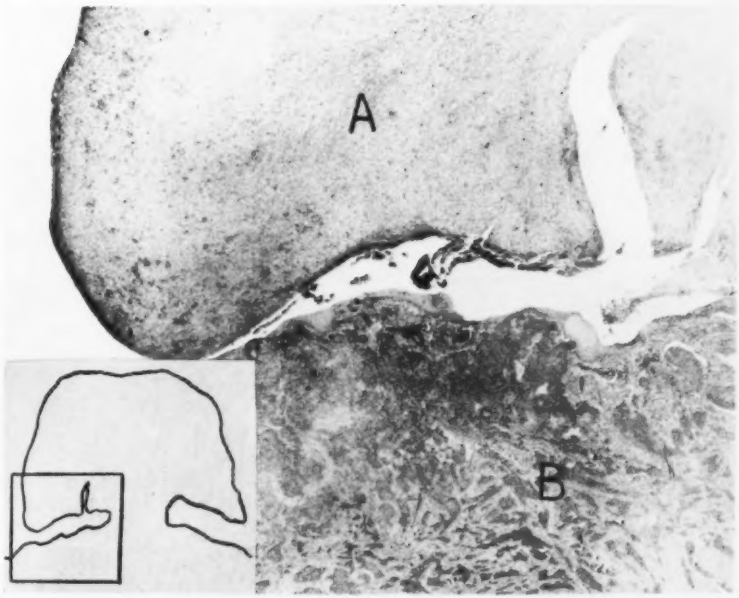

Figure 1. A cross section through the tumor and the base of the tongue. The insert shows a diagram of the entire lesion with the area in this section outlined. "A" is part of the large polypoid growth, while "B" shows nests of malignant squamous cell in various degrees of differentiation invading the base of the tongue. (× 30)

The interpretation of the sarcomatous elements (figs. 2 and 4) presented some difficulty. There was little question of malignancy, which was evidenced both by deep invasion of the tongue musculature (fig. 4) and by metastases to lymph nodes (fig. 5). In both the primary site and the metastases the appearance was the same: a markedly pleomorphic and fusiform arrangement that had the general appearance of a rhabdomyosarcoma. However, cross striations were visible in

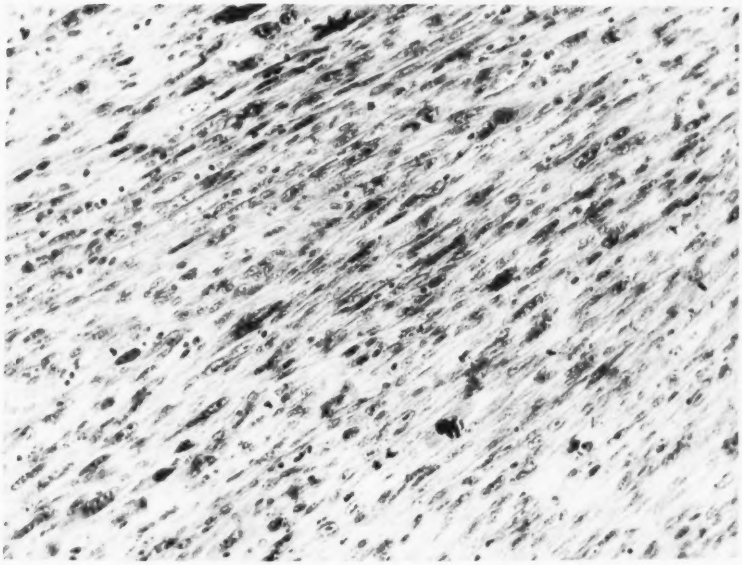

Figure 2. Photomicrograph of area "A" in figure 1. The fusiform arrangement, as well as the marked pleomorphism, can be seen easily. (× 100)

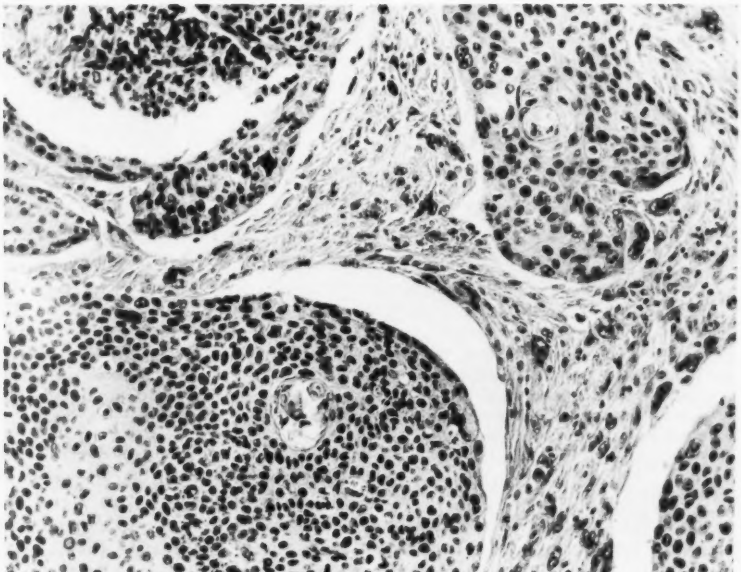

Figure 3. Photomicrograph of area "B" in figure 1. Nests of malignant squamous cells in the substance of the tongue are visible. (× 100)

only a rare cell, making this diagnosis questionable. Special stains, such as Masson's trichrome and reticulum stains, indicated that the

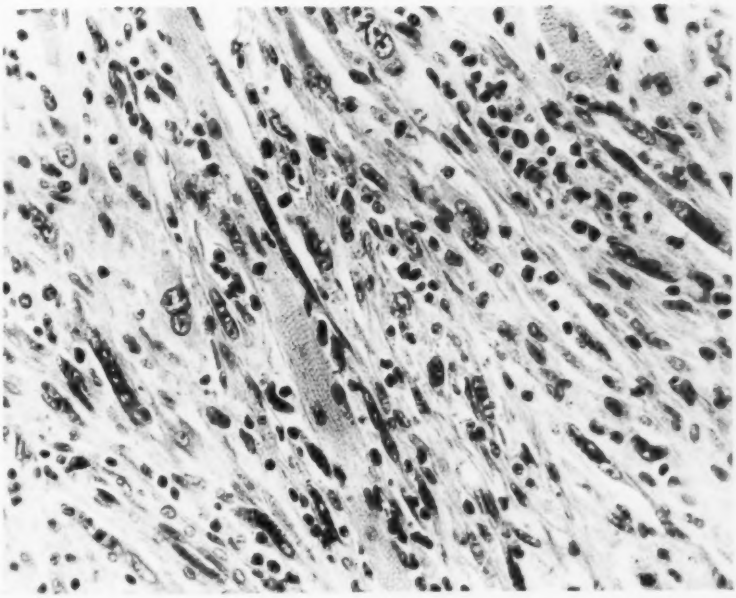

Figure 4. Sarcomatous tissue deep within the tongue musculature. Remnants of muscle fibers of the tongue are visible in the center of the figure. (× 200)

tumor was a sarcoma of muscle origin rather than a fibrosarcoma. The diagnosis, therefore, was either a leiomyosarcoma or an undifferentiated rhabdomyosarcoma.

DISCUSSION

Multiple tumors of the carcinosarcoma type have been classified by Saphir and Vass[3] as follows:

1. Composition tumors in which both the parenchyma and stroma have become malignant.
2. Combination tumors in which two different growths develop from a single stem cell.
3. Collision tumors in which two independent tumors are present and mutually invade each other.

Many of the tumors so reported fall into the first two types in which both elements are intimately mixed. Many of these have been shown to be markedly undifferentiated carcinomas giving the appearance of sarcomas.[2,3] The sarcomatous parts of other tumors are thought to represent benign changes in the

supporting stroma, giving the appearance of a sarcoma but without the ability to metastasize.

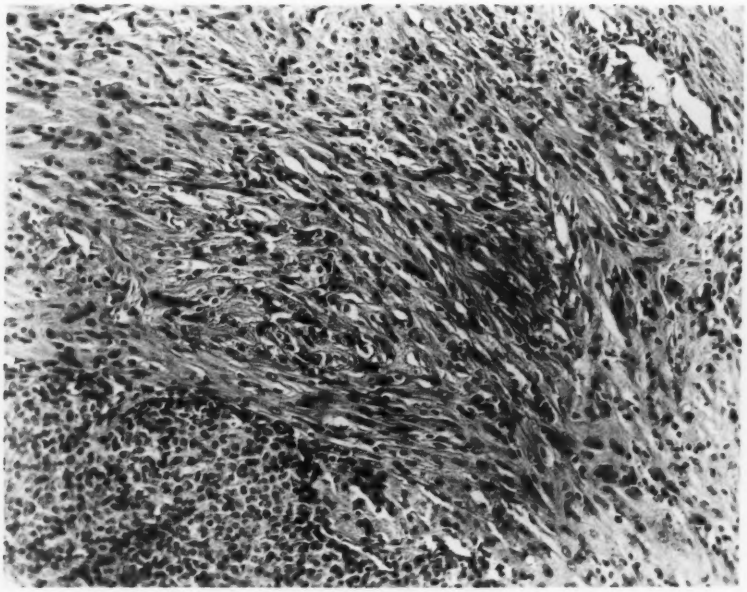

Figure 5. An area of sarcomatous tissue within a lymph node. The lymph node structure appears at the upper right, while the thickened capsule is at the left. The fusiform arrangement of the tissue between can be seen. (× 100)

Lane[3] recently reported a series of 10 cases similar to the one presented here. They were large, polypoid, sarcomatous growths associated with an adjacent carcinoma. It was his opinion that the sarcomatous elements were benign, reactive changes in the stroma without the ability to metastasize. The term "pseudosarcoma" was thus applied to these growths. Although the present case is very similar to those reported by Lane, it is of some interest in that a frank metastatic sarcomatous lesion was identified in a lymph node. It is true, however, that the squamous-cell carcinoma is represented in the nodes to a much greater extent than the sarcoma. In this situation the possibility has been raised that the carcinoma, which in some manner caused the development of a "pseudosarcoma" at the primary site, may cause a similar pseudosarcomatous change in the stroma adjacent to a metastasis.[3] The present case, however, is a sarcoma of muscle origin, and the elements found

invading deeply into the tongue musculature and as metastases in a lymph node are of the same type. It seems more likely,

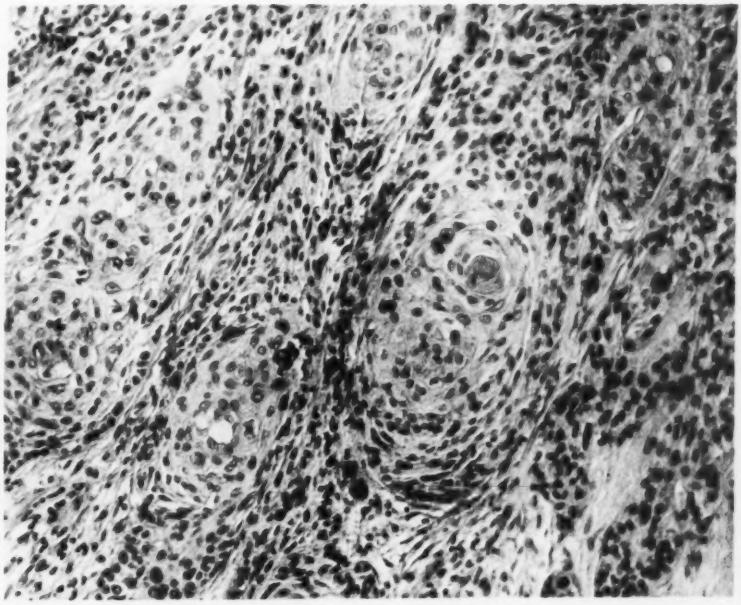

Figure 6. Photomicrograph of an area of squamous-cell metastases within the same node. (× 100)

therefore, that this is a metastasis rather than a benign transformation of lymph node stroma.

SUMMARY

The case presented is an unusual form of collision tumor in which both elements have metastasized. The epithelial component is a squamous-cell carcinoma. The sarcomatous elements have been shown to be of muscle origin, and show both deep invasion and distant metastases to nodes.

ACKNOWLEDGMENT: The authors wish to express their appreciation to Capt. Robert B. Brown, MC, USN, Chief of Surgery at the U. S. Naval Hospital, Bethesda, Md., for his helpful suggestions relating to the preparation of this paper.

REFERENCES

1. Frank, I., and Lev, M.: Carcinosarcoma of larynx. *Ann. Otol., Rhin. & Laryng.* 49: 113-129, Mar. 1940.

2. King, A., and Koerner, T. A.: Carcinosarcoma of esophagus. *Surgery* 42: 389-393, Aug. 1957.

3. Lane, N.: Pseudosarcoma (polypoid sarcoma-like masses) associated with squamous-cell carcinoma of mouth, fauces, and larynx; report of 10 cases. *Cancer* 10: 19-41, Jan.-Feb. 1957.

4. Pearlman, S. J. (Chicago): So-called carcino-sarcoma of esophagus. *Ann. Otol., Rhin. & Laryng.* 49: 805-820, Sept. 1940.

5. Saphir, O., and Vass, A.: Carcinosarcoma. *Am. J. Cancer* 33: 331-361, July 1938.

6. Taylor, H. E., and Rae, M. V.: Endobronchial carcinosarcoma. *J. Thoracic Surg.* 24: 93-100, July 1952.

7. Thompson, J. R.: Carcinosarcoma of esophagus; report of case with autopsy findings. *J. Thoracic Surg.* 25: 261-264, Mar. 1953.

TREATMENT OF HEMORRHOIDAL DISEASE

In current medical literature there are few articles on the subject of hemorrhoidectomy and those that do appear concern only technique. There seem to be no attempts to study the results of the operation or to compare the effectiveness of operative treatment with nonoperative treatment of the disease.... The crucial question is whether the operation is being done for good reasons. Indications for the operation which are given in modern textbooks appear to be sound but they should obviously not be broadened to include all patients with symptomatic hemorrhoids who come under the care of an occasional surgeon. Any surgeon not manifesting a primary interest in proctology who does a large number of hemorrhoidectomies is a fair target for criticism. Many of his patients who have hemorrhoids could doubtless be treated successfully by conservative methods alone. They may need nothing more than some good advice about personal hygiene and perhaps a few days of bed rest. A careful soap and water cleaning of the anus after each bowel movement, or at least once a day, is effective in clearing the chronic infection that is generally recognized as the usual cause of painful hemorrhoids. If the hemorrhoids are large, they shrink rapidly when the favorable hemodynamics provided by bed rest are added to a regimen of cleanliness. Is it possible that the painstaking care given to these patients after a hemorrhoidectomy in order to obtain a rapid convalescence would cure most of them even without an operative procedure? A comparison of this course of therapy with the operative treatment would doubtless be enlightening.

—F. JOHN LEWIS
in *Surgery*
p. 431, August 1958

Perforated Meckel's Diverticulum in a Three-Month-Old Infant

CLARENCE R. HIGGINS, *Captain, USAF (MC)*
GILBERT F. MUELLER, *Captain, USAF (MC)*

IT IS well known that Meckel's diverticulum can give rise to serious complications, especially when it becomes manifest in the pediatric age group. A case is described to illustrate the serious nature of these complications in the infant, and discusses briefly the clinicopathologic picture.

CASE REPORT

A 3-month-old infant was seen in September 1957 at this hospital because of blood in the stools. He was in good health until the day of admission when the mother noticed three stools containing blood. One of the stools consisted almost entirely of dark blood. Others were dark blood mixed with stool. The infant was asymptomatic and appeared happy. There was no history of vomiting, loose stools, or episodes of crying.

Initial physical examination revealed a healthy-appearing infant without pallor and in no apparent distress. His rectal temperature was 100.4°F. Results of examination of the abdomen were negative. Rectal examination revealed formed stool mixed with dark blood.

Admission laboratory tests revealed a white blood cell count of 13,300 per μl, with 31 per cent neutrophils, 2 per cent band forms, 64 per cent lymphocytes, and 3 per cent eosinophils; hemoglobin was 9.8 grams. Urinalysis was negative.

A flat roentgenogram of the abdomen showed no abnormality. A tentative diagnosis of Meckel's diverticulum or intestinal polyp was made.

The following morning, while being examined, the infant suddenly began to scream as if he were in pain, and flexed his legs on his abdomen periodically. The abdominal findings changed. There was muscle spasm and apparent tenderness to palpation in the right periumbilical area. No definite mass was palpable. A barium enema was given. The barium flowed to the cecum without delay or obstruction. However, despite attempts with increased hydrostatic pressure and

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From U. S. Air Force Hospital, Castle Air Force Base, Calif.

palpation, the terminal ileum could not be filled. The small bowel was not distended. A repeat white blood cell count showed 20,000 per μl, with 87 per cent neutrophils. Further roentgenograms prior to surgical intervention revealed small bowel distention and an oval collection of barium in the cecum, with definite concave border suggestive of an ileocecal intussusception.

Abdominal exploration through a right rectus incision 12 hours after the onset of acute abdominal symptoms revealed a localized area in the ileal region containing serosanguineous fluid, which was not foul smelling, and the omentum adherent to an acutely inflamed 1.5-cm Meckel's diverticulum. There was no evidence of an intussusception. Removal of the omentum revealed a necrotic, perforated ulcer at the base of the diverticulum measuring 2 mm in diameter. A yellowish fluid exuded from the perforation, suggestive of gastric secretion. The diverticulum was clamped at its base and removed. The appendix was not seen or searched for. Penicillin and streptomycin sulfate were instilled into the abdominal cavity and the abdomen was closed. A subcutaneous drain was left in place. Postoperatively, the infant was placed on high dosage of antibiotics and his temperature returned to normal on the second day. Oral feedings were instituted on the third day, and he was discharged the 12th day after surgery.

Histopathologic examination revealed the presence of acute inflammatory changes with perforation at the base of the diverticulum. Gastric mucosa was demonstrated in the wall of the diverticulum.

DISCUSSION

In addition to the normal intestinal mucosa, a diverticulum may contain heterotopic gastric mucosa, pancreatic tissue, or duodenal glands (Brunner's glands), either in the wall or in the form of polypoid accumulations of these tissues; 25 per cent of all Meckel's diverticuli contain heterotopic tissue, most often gastric in type.[1] The gastric tissues are capable of secreting hydrochloric acid and pepsin. The secretion usually begins synchronously with the gastric activity. Thus, all mucosa-like structures in the diverticulum are exposed to these digestive juices at a time when food and intestinal juices are not present to act as buffers.

Three distinct types of pathologic changes may occur when a Meckel's diverticulum is present, producing three main groups of symptom complexes: (1) ulceration with or without perforation, (2) infection resulting in diverticulitis, and (3) intestinal obstruction. In addition, fistula formation which must be differentiated from a patent urachus and rare tumors can occur.

First, ulceration with or without perforation. Heterotopic gastric mucosa is of paramount importance for, as it is capable of producing hydrochloric acid and pepsin, it is responsible for the

peptic ulceration that occurs in such cases. The ulcers are commonly observed at the base of the diverticulum and may produce perforation, hemorrhage, or both. This case is an illustration in point for the facts stated above. That hemorrhage and perforation occurred within three months of the birth of this infant attests to the susceptibility of the ileal mucosa when exposed to gastric secretions, unbuffered by food, biliary and pancreatic juices. When bleeding occurs, nearly 100 per cent of the specimens probably will show gastric mucosa on careful examination, according to Berman, Schneider, and Potts.[2] Gastric mucosa was demonstrated in the microscopic analysis of the diverticulum in this case. The hemorrhage, without associated abdominal pain, is typical of a Meckel's diverticulum, and is the single most common finding.[3] The occurrence of rectal bleeding, greater in amount than usually seen with polyps or fissures, plus the dark color and the fact that blood is mixed with stool, is the usual finding. The absence of mucoid material, which causes jelly-like or currant-jelly stool, is another helpful point to differentiate a Meckel's diverticulum from intussusception.

Second, infection resulting from diverticulitis. Meckel's diverticulum may be the seat of inflammatory changes which may be acute or chronic and may closely simulate acute appendicitis.[4] Perforation may occur, but is nearly always caused by the presence of gangrene in the diverticulum. When perforation results from peptic disease, gangrene is absent.

Third, obstruction. Meckel's diverticulum may be the cause of intestinal obstruction. It may act as an axis about which loops of bowels rotate to form a volvulus. Or it may be followed by a band that adheres to any peritoneal surface, forming an opening through which many various forms of intestinal strangulation may take place. On the other hand, Meckel's diverticulum may be the leading point of an intussusception.

SUMMARY

A single case of Meckel's diverticulum, with hemorrhage and perforation, in a 3-month-old infant, with successful treatment, is presented, followed by a brief discussion.

REFERENCES

1. Grossman, J. W.; Fishback, C. F.; and Lovelace, W. R., II.: Hemorrhage from Meckel's diverticulum as cause of melena in infancy; report of case in which diverticulum was demonstrated roentgenographically. *Radiology* 55: 240-242, Aug. 1950.

2. Berman, E. J.; Schneider, A.; and Potts, W. J.: Importance of gastric mucosa in Meckel's diverticulum. *J. A. M. A.* 156: 6-7, Sept. 4, 1954.

3. Benson, C. D., and Linkner, L. M.: Surgical complications of Meckel's diverticulum in infants and children; analysis of 60 cases. *A. M. A. Arch. Surg.* 73: 393, Sept. 1956.

4. Brookes, V. S.: Meckel's diverticulum in children; report of 43 cases. *Brit. J. Surgery.* 42: 57-68, July 1954.

The Fate of Bone Graft Replacement in Monostotic Paget's Disease

H. TODD STRADFORD, *Captain, MC, USN*

PAGET'S DISEASE of bone (osteitis deformans) is described in the literature frequently, but there are few reports on the surgical treatment, and even a greater paucity in regard to the fate of bone grafts. In 1918, Abbe[1] reported surgical repair of a grossly deformed maxilla, with excellent healing and restoration of function. In his article there is a photograph of a tibia deformed by monostotic Paget's disease. He may have been suggesting surgical repair, but he makes no mention of this idea in his article. In reviewing the literature, Kanavel[2] (in 1907) and New and Harper[3] (in 1933) found that at frequent intervals surgical intervention had been advocated in cases of Paget's disease of facial bones. The opposite has been true in bones of the extremities.

Trinca[4] of Australia and Brocq, Layani, and Thoyer-Rozart of France[5] recommended correction of deformities by osteotomy. Amputation was suggested by Charbonnel and Doche[6] in the French literature, and by Wanke[7] in the German literature. This was mainly for malignancy. Stein[8] suggested osteotomy as the treatment of choice but admitted that the deformities and disease continue.

This case presents the fate of a bone graft in a patient with proven Paget's disease. I do not advocate this method of treatment for all deforming Paget's disease, but where a deforming monostotic lesion presents, it offers more than a transitory osteotomy.

CASE REPORT

In December 1948 a 19-year-old man was referred to the orthopedic service of a naval hospital because of a painful left forearm of 4 years' duration. Onset had been insidious. The forearm had gradually become bowed on the radial side. Past history revealed that in 1946 the patient had been admitted to the hospital because of severe pain of 6 months' duration. A biopsy had been performed at that time but no specific diagnosis had been made.

From U. S. Naval Hospital, Bethesda, Md., Capt. Stradford is now assigned to Armed Forces Institute of Pathology, Washington, D. C.

Roentgenograms on 11 January 1949 revealed a grossly deformed bone with a moth-eaten appearance, but without loss of cortical integrity (fig. 1). Laboratory studies revealed normal findings, with calcium and phosphorus within normal limits; alkaline phosphatase ranged from 6 to 9.4 Bodansky units.

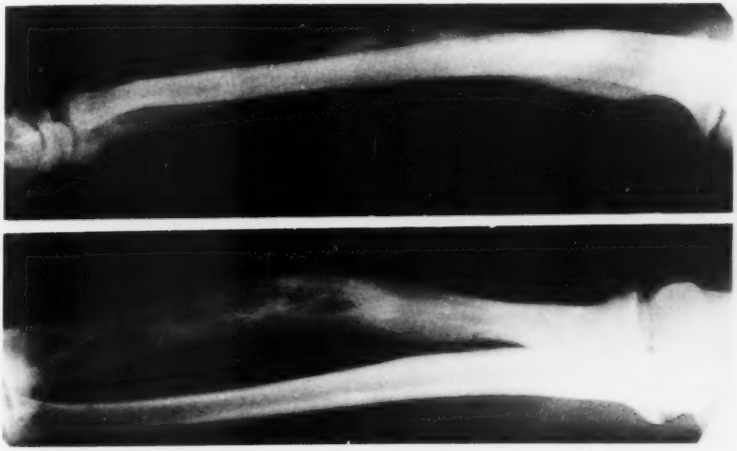

Figure 1. Monostotic Paget's disease of four years' duration.

A biopsy revealed typical Paget's disease. Roentgenographic survey of the skeleton failed to reveal any additional foci. Because of the patient's pain and the apparent monostotic nature of the disease, it was decided to excise the affected portion of the radius and replace it with a graft.

The only previous bone graft in a similarly affected bone had been a small onlay graft, in the treatment of a fracture, which became incorporated into the parent bone and also was affected by the disease. This case was an opportunity to determine if a major graft might escape this fate. Consequently, a tibial cortical graft was chosen because its replacement would entail complete reorganization.

Through a Henry's approach, the radius (fig. 2) was excised from above the bicipital tubercle to within 2 cm of the wrist joint. The autogenous graft was slotted and mortised into place, (fig. 3), and no internal fixation other than soft tissue closure was utilized. The stability was tested by lifting the arm from the table by the graft.

The patient did well, and after a convalescence of six months returned to duty. In the next 10-year period he was seen periodically. Roentgenograms made 5 years postoperatively showed the cortical graft completely reorganized with a medullary canal. In spite of Paget's disease continuing in the parts of the radius remaining from the original bone, the graft had remained unaffected. General roentgeno-

graphic recheck in a 10-year-follow-up, however, revealed some invasion of the graft from the end abutting onto the old bone affected by Paget's disease (fig. 4). There are also changes in the lumbar

Figure 2. The excised radius sawed in half, longitudinally.

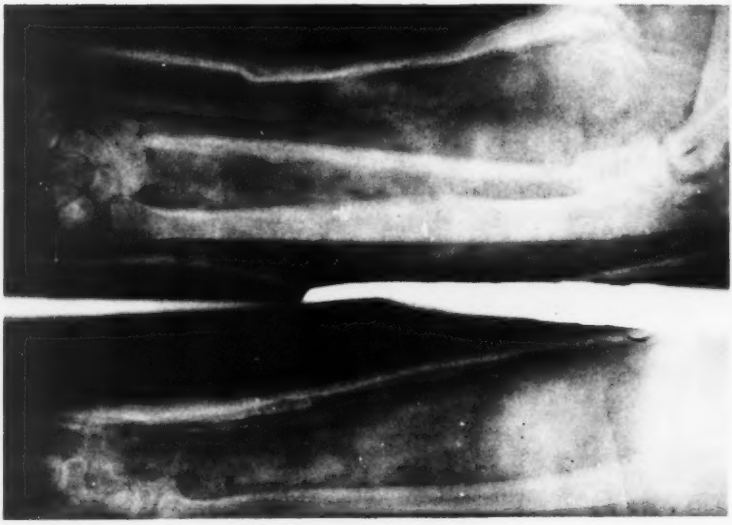

Figure 3. Immediate postoperative roentgenograms, showing graft in place.

vertebrae and femurs. The ulna which protruded into the wrist was intended to be resected at a later date, allowing biopsy of the radius and graft, but the arm has remained asymptomatic and the patient,

now a Chief Petty Officer on active duty, is satisfied with his wrist without further treatment.

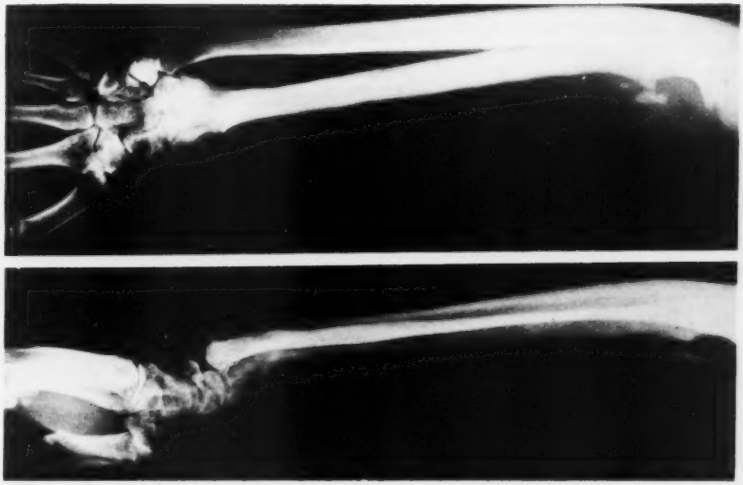

Figure 4. Radius, 10th year following surgery, showing the graft completely reorganized. Note reformation of medullary canal. Paget's disease persists in old bone left at wrist. Slight invasion of the graft is considered to be by direct extension from the old remaining focus.

SUMMARY AND CONCLUSIONS

The point of interest in the case presented is the fact that an autogenous cortical graft used to replace a radius affected by Paget's disease survived in normal function for 10 years. The graft was completely replaced and reorganized to develop a medullary canal. The portion of the graft with involvement is obviously invading from a known focus. This suggests that whatever causes Paget's disease is inherently within the affected bone, and by excision of the affected bone, the disease is eliminated for a time locally. This points negatively to a systemic origin for Paget's disease. This case reveals the need for more experimental work on this disease. Early surgical intervention in long bone deformities that are proceeding rapidly is worthy of consideration.

REFERENCES

1. Abbe, R.: Paget's disease of bone; excellent repair after surgical operation. *J. A. M. A.* 70: 371-372, Feb. 9, 1918.

2. Kanavel, A. B.: Surgical intervention in leontiasis ossea. *Surg., Gynec. & Obst.* 4: 719-734, June 1907.

3. New, G. B., and Harper, F. R.: Osteitis deformans affecting bones of face. *Am. J. Surg.* 22: 500-506, Dec. 1933.

4. Trinca, A. J.: Surgical treatment of osteitis deformans. *M. J. Australia* 1: 591-592, May 4, 1929.

5. Brocq, P.; Layani; and Thoyer-Rozat, J.: A propos d'un cas d'ostéotomie correctrice du fémur dans une maladie de Paget. *Mem. Acad. de chir.* 66: 34-41, Jan. 3-10, 1940.

6. Charbonnel and Doche: Sur un cas d'osteite diffuse generalisee de nature indeterminee, ayant necessite une desarticulation du membre interieur gauche. *Arch. Fr. Belg. Chir.* 1933-1934.

7. Wanke, R.: Ostitis deformans Paget als präsarkomatöses Leiden. *Monatsch. f. Krebsbekämpf.* 1: 366-373, Sept. 1933.

8. Stein, I.: Surgery in treatment of complications of Paget's disease. In *Clin. Orthopedics* 1: 225-230, 1953.

THE CHALLENGE AND THE RESPONSIBILITY

"Present-day disaster planning includes a challenge to us to study the biological effect of radiation—whole-body irradiation with gamma rays, neutrons, and protons. Any person will die if he gets enough exposure; the only treatment we have now is rest and aspirin. Medical science must make progress to improve our understanding of radiation effects and to develop effective treatment. The responsibility should be accepted and a better answer found soon."

—JOSEPH R. SHAEFFER, Col., MC, USA
in *Proceedings of the Staff Meetings of the Mayo Clinic*
p. 145, Mar. 19, 1958

HEALTH OF THE AMERICAN INDIANS

"The health status of the American Indian is, in general, that of any underprivileged group. The high disease indices always quoted pertain to those remaining on reservations and not to the thousands who have become a part of the dominant culture. There appears to be no predilection for certain diseases, but rather we observe the high rates in diseases identified with low economic resources. Those of us in the Indian health program feel that the socio-economic disadvantages prevalent among the Indians must be solved concomitantly with any marked improvement in their health status. In spite of the deficiency in such necessities as housing, clothing, food, transportation, and so forth, we find real concern among the Indians in regard to health matters and an increasing acceptance of recognized health procedures."

—HERBERT A. HUDGINS, M. D.
in *Journal Lancet*
p. 108, March 1958

Fractures of the Capitate Bone

JOHN J. RIEDER, *Captain, MC, USN*

FRACTURES of the capitate bone are relatively rare. The earliest reported case was by Gouldesbrough,[1] who in 1916 described a fracture of the navicular and capitate in a 10-year-old boy. Fenton and Rosen[2] in 1950 found only three cases on record at the Hospital for Joint Diseases. Such fractures are of two main types, the most common being a fracture through the waist as a result of massive force applied with the wrist in a neutral position. The other type is associated with a fracture of the navicular bone, and occurs in the proximal portion of the capitate. According to Fenton,[3] the wrist is forced into radial deviation, causing a fracture of the navicular. As the force is continued, the proximal portion of the fractured navicular impinges against the capitate, fracturing it and rotating the proximal fragment 180°. The following cases illustrate fractures of both types.

Figure 1 (case 1). Roentgenogram showing partly healed fracture of capitate bone and fresh fracture of hamate.

From U. S. Naval Hospital, Oakland, Calif. Capt. Rieder is now assigned to U. S. Naval Hospital, Great Lakes, Ill.

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Figure 2 (case 1). Roentgenogram showing fracture of capitate healed and that of hamate partly healed.

CASE REPORTS

Case 1. A 20-year-old aviation apprentice was injured in May 1956 when he tripped over a ladder and fell on his outstretched left wrist. Following this, he noticed some weakness of his left hand and limitation of palmar flexion. On 19 November 1957 he again fell and injured his left wrist. Roentgenograms at this time showed fractures of the capitate and hamate bones (fig. 1). The capitate fracture appeared to be an old injury, as there was some sclerosis around the fracture site. A navicular type of short arm-cast was applied for three months, at the end of which roentgenograms revealed the fractured capitate to be healed (fig. 2). The patient was then placed on physical therapy and regained a normal range of wrist motion.

Case 2. A 20-year-old seaman recruit injured his right wrist in February 1957 by falling from a platform. Initial roentgenograms showed a fracture of the navicular and a fracture of the capitate with the proximal fragment rotated 180° (fig. 3). The patient was treated with a navicular type of short arm-cast for eight months. Roentgenograms taken at this time revealed the fractured navicular to be healed. The proximal portion of the fractured capitate was still rotated 180° (fig. 4).

The patient was then treated with physical therapy, and at the time of return to duty motion of the wrist was as follows: volar flexion,

50°; dorsiflexion, 35°; ulnar deviation, 35°; and radial deviation, 35°. The wrist was asymptomatic.

Figure 3 (case 2). Roentgenogram showing fractures of navicular and capitate bones, with proximal fragment of capitate rotated 180°.

DISCUSSION

The treatment of fractures across the waist of the capitate was described by Speed[4] as consisting of immobilization of the forearm and hand in straight extension for four weeks. Inasmuch as the patient in case 1 appeared to have an old fracture, immobilization was continued until union was complete, and the patient had a satisfactory result. Treatment of fractures involving rotation of the proximal portion of the capitate was described by Fenton and Rosen[2] as excision of the rotated fragment. It was their opinion that this was necessary because

Figure 4 (case 2). Roentgenogram showing healed fracture of navicular bone. Proximal portion of capitate is still rotated 180°.

it was avascular. Jones[5] recently reported a case treated by immobilization, in which the fracture healed with the proximal fragment rotated 180°. In case 2, the patient's wrist was asymptomatic and excision of the proximal fragment was deferred. There was some indication that the rotated fragment of the capitate had become adherent to the navicular.

REFERENCES

1. Gouldesbrough, C.: Case fracture of scaphoid and os magnum in a boy 10 years old. *Lancet* 2: 792, Nov. 4, 1916.

2. Fenton, R. L., and Rosen, H.: Fracture of capitate bone--report of 2 cases. *Bull. Hosp. Joint Dis.* 11: 134-139, Oct. 1950.

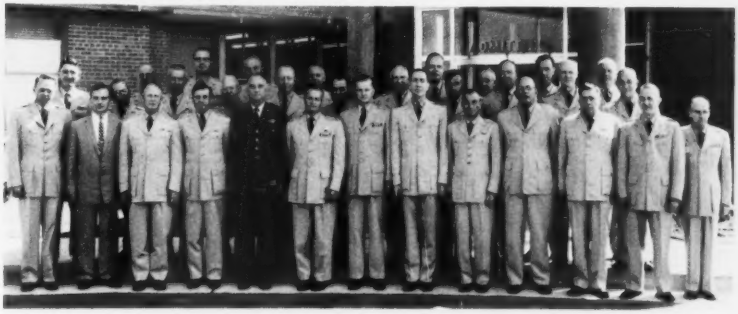
3. Fenton, R. L.: Naviculo-capitate fracture syndrome. *J. Bone & Joint Surg.* 38-A: 681-684, Apr. 1956.

4. Speed, K. *Traumatic Injuries of the Carpus.* D. Appleton & Company, New York, N. Y., 1925.

5. Jones, G. B.: Unusual fracture-dislocation of carpus. *J. Bone & Joint Surg.* 37-B: 146-147, Feb. 1955.

U. S. AIR FORCE NATIONAL CONSULTANTS, COMMAND SURGEONS MEET AT ANDREWS AFB

The annual conference of the Air Force command surgeons and national consultants to the Surgeon General was held during the first week of September in the new hospital at Andrews Air Force Base near Washington, D. C. This three day meeting, according to Major General Dan C. Ogle, USAF (MC), Surgeon General of the Air Force, provides an interchange of the latest military and civilian medical thinking and technics. It is a part of the program of the Air Force Medical Service to ensure the best possible professional care in hospitals and dispensaries.



Shown above are the staff surgeons of the Air Force Commands in the United States and overseas. Below is the group of national consultants in the various medical and surgical specialties.

THREE WELL-KNOWN OFFICERS RETIRE

Three prominent Medical Corps officers of the Army, Navy and Air Force retired recently with a combined total of more than 90 years of military service.

Gen. Maxwell

Capt. Kellum

Gen. Van Brunt and Col. Mudgett

Brigadier General Earl Maxwell, USAF (MC), left the post of chief of the medical division in the office of the Air Force Inspector General to join the Alcon Laboratories, Fort Worth, Texas. He was formerly surgeon of the Alaskan Air Command.

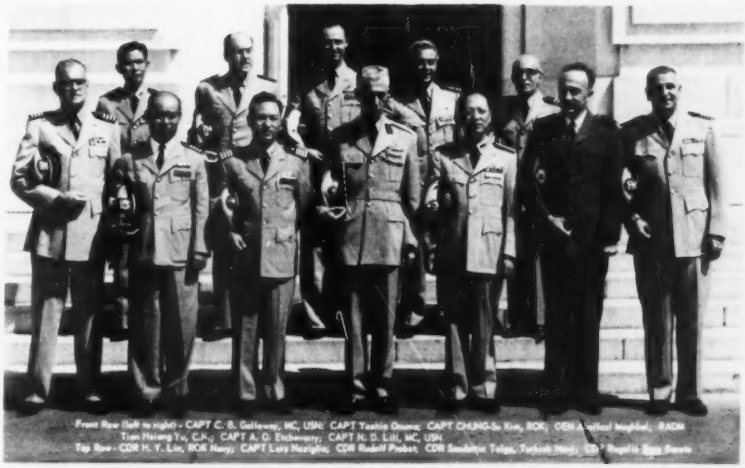
Captain Wilbur E. Kellum, MC, USN, former commanding officer of the Naval Medical Research Institute, Bethesda, Maryland, retired in the grade of commodore on 30 September. Dr. Kellum served as the commanding officer of the U. S. Naval School of Aviation Medicine from 1947 to 1950. He was president of the Aero Medical Association from 1949 to 1950, and is the recipient of the John Jeffries and the Theodore Lyster Awards for outstanding achievement in aviation medicine.

Colonel Charles S. Mudgett, MC, USA, was retired on 28 August in a colorful ceremony at Ft. George G. Meade, Maryland, where he had been post surgeon and hospital commander since 1954. He was presented with the Legion of Merit by Major General Rinaldo Van Brunt, Chief of Staff, Second U. S. Army, for his "keen perception, resourcefulness and exceptional professional competence. . .in the performance of outstanding service." He has joined the staff of the Pennsylvania State Health Department, Division of Tuberculosis Control, Harrisburg.

FOREIGN OFFICERS ATTEND NAVY COURSES

Twenty-two Naval medical officers of twelve nations are enrolled in special training courses in hospital management and preventive medicine at the U. S. Naval Medical School, Bethesda, Maryland. The courses, which are of ten weeks' duration, will be completed in November.

Shown above are the foreign students taking the course in preventive medicine. Below is the group enrolled in the course of hospital management.


Front Row (left to right) - CAPT C. B. Galloway, MC, USN; CAPT Yoshio Ohuma; CAPT CHUNG-Su Kim, ROK; CDR Abdul Majeed, RADN
Tien Heiang Yu, C.N.; CAPT A. O. Etcheverry; CAPT N. S. Lill, MC, USN
Top Row - CDR H. Y. Lin, ROK Navy; CAPT Luis Nazigito; CDR Rudolf Probst; CDR Souleiman Tolga, Turkish Navy; LT Angelo Egas Bueno

A MESSAGE FROM THE A. M. A.

There has been a growing interest in emergency medical service by many persons in the health services. For the past 12 years, the Council on National Defense has made information available to physicians on the various aspects of civil defense. Since February 1955 with the formation of the Council's Committee on Civil Defense, the entire activities related to disaster medicine have come under the scope of the Committee.

The American Medical Association activities in the field of civil defense are in four general areas: organizational, informational, assistance to training programs, and liaison. There has been a continuous program in all fields by the Committee within the limitations of staff personnel and budgets. Following is a brief outline of the action programs.

1. **Organizational.** The A. M. A. has exerted leadership in urging state and local medical societies to develop organizations within themselves to effectively handle any type of medical emergency. Through meetings, letters, questionnaires and personal visits by the staff of the Council, some type of emergency medical care organization has been achieved in 48 state societies, Hawaii, and the District of Columbia as well as in some local medical societies. Recently, the series of regional civil defense meetings by the Committee with the executive secretary of the state medical societies, the chairmen of the state societies emergency medical service committees and their counterparts in the women's auxiliary has brought the necessity for proper local and regional organization to the attention of the states. In addition, the Committee has repeatedly urged state and local medical societies to become active in state and local civil defense organizations.

The A. M. A. has also been active in developing a medical civil defense team consisting of all responsible elements of the medical and health personnel in a community. As the result of this forward-looking action, it was possible with the assistance of the Department of the Army and the co-operation of the Office of Civil and Defense Mobilization (formerly the Federal Civil Defense Administration) and the Federal medical services to field test critically some of the medical equipment that would be used in disaster.

The creation of a Commission on a National Emergency Medical Care Plan by the A. M. A. upon request of FCDA to make a national study of medical care of a nation before, during, and after nuclear warfare is another important contribution of the

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From the Council on National Defense of the American Medical Association. The views and opinions expressed are not necessarily those of the Department of Defense. —*Editor*

A. M. A. This study group is at work on a plan and it is anticipated will complete its report before the end of the year.

2. **Informational.** The major activity of the Committee has been the collection, development, reproduction, and dissemination of information concerning emergency medical care to the practicing physician. Nearly every type of medium has been used. National medical civil defense conferences have been held preceding the Association's annual scientific sessions since 1952. They have attracted leaders in civil defense from nearly all the states and have been a means of keeping current developments available to the physician. At the 1958 Annual Meeting in San Francisco, a panel discussion by the surgeons general or their deputies of the Military departments and the Public Health Service is an indication of the quality of programs given. The Association also assists in other programs. Publications include articles in the *Journal of the American Medical Association, Civil Defense Review,* informational memorandum, and materials for newsletters. Periodically, a bibliography of the medical aspects of civil defense, proceedings of annual medical civil defense conferences and reprints of *J. A. M. A.* articles are published. Upon request, packets of civil defense material from government and state civil defense organizations are also mailed to members or those interested in the subject.

3. **Assistance to Training Programs.** By means of the library of materials collected by the Committee on Civil Defense, through the use of special committees, task forces, and working parties of the Association, and by observation at field tests there has been developed an important resource that will assist groups undertaking training programs.

4. **Liaison.** Since the creation of the Council on 3 December 1945, there has been steady and close liaison between government medical services and the medical profession in matters of civil defense. The Association offers its services to the government for the dissemination of information in matters of civil defense, to assist in developing an interest in emergency medical care, in co-ordinating some aspects of the various activities of the medical services and other functions. In this manner the Association has been able to aid materially in the development of a sound civil defense. In addition, on many occasions, the Association has presented its views on the medical aspects of civil defense to committees of the Congress concerned with legislation in this field.

While much has been accomplished during the past 12 years and the beginnings of a medical civil defense has been made, a great deal more still remains to be done. The Committee on Civil Defense views this as a continuing problem, as never-ending as the professional study that each physician does daily.

CAPT. AVERY TO HEAD MEND PROGRAM

Captain Bennett F. Avery, MC, USN, editor of the *Journal* since 1 July 1955, has been appointed national coordinator of the Medical Education for National Defense (MEND) program. He has been succeeded by Colonel Robert J. Benford, USAF (MC), associate editor for the past 16 months.

Capt. Avery

Formerly dean of Boston University School of Medicine, Dr. Avery has held important medical posts in the Near East. He served as professor of anatomy, and later acting dean, of the medical school of the American University in Beirut, and from 1944 to 1949 was first Director General of and then Advisor to the Imperial Iranian Ministry of Health. His MEND offices will remain in the Navy Bureau of Medicine and Surgery where he has also held the position of chief of the publications division since 1952. His successor in that position is Captain Leslie B. Marshall, MC, USN (Ret).

Medical Civil Defense Emblem

A medical civil defense emblem for world-wide use has been proposed by a committee of representatives of the World Medical Association, the International Committee of the Red Cross and the International Committee of Military Medicine and Pharmacy. Its adoption by all countries will aid in the protection of medical personnel and equipment engaged in civil defense, according to Dr. Louis H. Bauer, secretary-general of the WMA. The emblem is red on a white background.

The new emblem

Tripler Army Hospital Anniversary

Tripler U. S. Army Hospital in Moanalua, T. H., marked its 10th anniversary of service on 10 September with a simple commemorative ceremony. The present, 1,500-bed hospital, under the command of Brigadier General Jack W. Schwartz, MC, USA, replaced a former hospital, built in 1906, later named Tripler General Hospital after Brigadier General Charles S. Tripler, medical director of the Army of the Potomac in the Civil War.

OFFICERS CERTIFIED BY SPECIALTY BOARDS

Supplementary Listing

The Surgeons General of the military medical services have announced that the following regular Medical Corps officers have been certified by the boards indicated since the listings published in previous issues of the *Journal*.

American Board of Pediatrics

James R. Upp, Capt., USAF

American Board of Obstetrics and Gynecology

Paul H. Stavig, Maj., USAF

American Board of Pathology

Pathologic Anatomy

Edward S. Brezina, Maj., USAF
James R. Clay, Capt., USAF
William E. Cowell, Lt., USN
Robert E. Pierce, Maj., USAF
David B. Rulon, Comdr., USN
Glenn A. West, Maj., USA

Clinical Pathology

William W. Ayres, Capt., USN
Edward S. Brezina, Maj., USAF
James R. Clay, Capt., USAF
Robert M. Dimmette, Comdr., USN
David B. Rulon, Comdr., USN

American Board of Ophthalmology

Ray M. Balyeat, Jr., Capt., USAF
Harold D. Easterly, Jr., Lt., USN
Walter A. Fairfax, Jr., Capt., USAF
Lawrence O. Gahagan, Capt., USAF
Victor M. Ohta, Capt., USAF
James I. Thorn, Comdr., USN

American Board of Surgery

Warren H. Brune, Maj., USA
Richard H. Hood, Jr., Maj., USAF
Harry P. Raymond, Jr., Capt., USAF
George E. Reynolds, Lt. Col., USAF

American Board of Neurological Surgery

Ernest J. Penka, Lt. Comdr., USN

American Board of Physical Medicine and Rehabilitation

Joel L. Roth, Maj., USA

American Board of Preventive Medicine

Aviation Medicine

Richard M. Fenno, Lt. Col., USAF
Oliver A. Mays, Lt. Col., USAF
Gordon H. Rhoades, Col., USAF
John R. Troxell, Lt. Col., USAF

Occupational Medicine

David H. Hersh, Capt., USN

OFFICIAL DECORATIONS

The following awards were recently announced by the Departments of the Army and Air Force.

Legion of Merit

Thomas W. Mattingly, Brig. Gen., MC, USA George Zinnemann, Lt. Col., USAF (MSC)

Air Force Commendation Medal

Donald R. Winkelblech, Maj., USAF (MSC)

Commendation Ribbon

James F. McNab, Maj., MSC, USA Robert I. Anderson, Maj., MSC, USA

Virchow Centennial Lecture Series

The Armed Forces Institute of Pathology, Washington, D. C., is celebrating the centennial of the publication of Rudolf Virchow's classic *Cellular-pathologie* with a series of lectures by staff members and guest lecturers. Interested persons are invited to attend the lectures on current research in this field to be given on 12 and 19 November, and 3 and 17 December.

DEATHS

CASTRO, Fred Edward, Major, VC, USAR, of South San Francisco, Calif.; assigned to the Fifth U. S. Army Veterinary and Food Inspection Service, Chicago, Ill.; graduated in 1941 from Agricultural and Mechanical College of Texas, College Station, Tex.; commissioned a major in the United States Army Reserve 18 November 1953; ordered to active duty 3 April 1954; died 30 July 1958, aged 43, at the U. S. Naval Hospital, Great Lakes, Ill., of bronchopneumonia.

DAINE, Donn David, Captain, MC, USA, of Iowa City, Iowa; assigned to Letterman Army Hospital, San Francisco, Calif.; graduated in 1956 from the State University of Iowa College of Medicine, Iowa City; commissioned a second lieutenant in the United States Army Reserve 15 November 1955; ordered to active duty 1 December 1955; commissioned a first lieutenant in the United States Army 1 July 1957; died 1 August 1958, aged 29, at San Mateo, Calif.

FLOREZ, Climaco, Captain, MC, USAR, of Forest Hills, Long Island, N. Y.; assigned to the U. S. Army Medical Center, Zama, Japan; graduated in 1950 from the Universidad Nacional Facultad de Medicina, Bogota, Colombia; commissioned a captain in the United States Army Reserve 22 December 1955; ordered to active duty 2 January 1956; died 12 August 1958, aged 35, in Japan, of coronary occlusion.

GIBBONS, Catherine Anne, First Lieutenant, USAF (NC), of Brooklyn, N. Y.; assigned to the U. S. Air Force Hospital, Lake Charles Air Force Base, La.; graduated in 1957 from the St. Catherine Hospital School of Nursing, Brooklyn, N. Y.; commissioned a first lieutenant in the United States Air Force Reserve 25 September 1957; ordered to active duty 3 November 1957; died 24 July 1958, aged 24, at the U. S. Air Force Hospital, Lake Charles Air Force Base, of a cerebral hemorrhage.

Reviews of Recent Books

ORTHOPEDIC DISEASES, Physiology—Pathology—Radiology, by *Ernest Aegerter*, M. D., and *John A. Kirkpatrick*, Jr., M. D. 602 pages; illustrated. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $12.50.

This volume fulfills a recognized need for a ready reference to the "basic science" aspect of orthopedic diseases. These afflictions are viewed from the standpoint of the altered physiology and morphology which in turn are related to the clinical manifestations and x-ray findings. The material is a well-organized compilation of published reports, stressing the rudiments of basic sciences and a simple classification of the diseases. The chapters are orderly arranged and divided into four sections. The first section reviews basic anatomy, physiology, histology, and radiology as applied to the skeletal tissues. The remaining three sections conveniently group diseases of the skeletal tissues into disturbances during development, diseases of the normally formed skeleton, and connective tissue tumors. Illustrations are carefully selected and informative, especially the reproductions of microscopic sections. Value of the work lies in the availability of this material in a compact volume for practical usage. It is highly recommended for the practicing orthopedic surgeon, the radiologist, the pathologist, and especially the orthopedic resident.

—EARL W. BRANNON, Col., USAF (MC)

A TEXT ON SYSTEMIC PATHOLOGY, Volume I, edited by *Otto Saphir*, M. D. 865 pages; with over 800 illustrations. Grune and Stratton, Inc., New York, N. Y., 1958. Price $32.

This text on systemic pathology is the first of a contemplated two-volume edition. It is edited by a respected authority in the field of general pathology with 11 collaborating authors, most of whom previously had been affiliated with the editor in research or academic pathology. One of the guiding motives for this work was to provide the medical student and the practicing hospital pathologist with more specialized information than is usually found in general textbooks on pathology. Also, it was hoped that by including references to important clinical signs and symptoms and to functional aberrations encountered in the course of a particular disease, that the pathology would be elevated above the realms of strict morphology and become "alive" and of interest to both the clinician and the pathologist.

This volume of 10 sections is largely a one-man book, having been written by the editor with the exception of sections on congenital heart disease by Dr. Maurice Lev, hermaphroditism and pseudohermaphroditism by Dr. Jay Gould, and the hematopoietic system by Dr. Ira Gore. For the most part the text is very well written, quite inclusive, clear, concise and practical. Occasional inaccuracies are noted and debatable statements are sometimes made. The illustrations, all in black and white are ample, and in general of good quality.

The inclusion of roentgenograms and angiocardiographs would have improved the section on congenital heart disease.

This reviewer is impressed with the fund of information in this volume. Some infrequently encountered disease conditions, rarely mentioned in other textbooks of pathology, are included here and given due attention. Frequently short biographical sketches of important figures in the field as well as an explanation of the derivation of many of the terms used in pathology add much to the interest of the reader. The number of references is large. These two volumes, if this first one can be considered typical, should take a deserved place among the better and more useful textbooks of pathology.

—*WILLIAM M. SILLIPHANT, Capt., MC, USN*

FUNCTIONAL BRACING OF THE UPPER EXTREMITIES, edited by *Raymond E. Solars.* Written and illustrated by *Miles H. Anderson,* Ed. D. Foreword by *Charles O. Bechtol,* M. D. 463 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $9.50.

This informative book is an outgrowth of a training program sponsored by the Prosthetics Research Board of the National Academy of Sciences, and was written to enable a more general dissemination of the rationale, technic, and principles involved in the prescribing, manufacture, and fitting of upper extremity functional braces to individuals suffering from some degree of upper extremity paralysis. There are sections on the functional anatomy of the hand, basic and functional anatomy of the arm and shoulder, the biomechanics of functional hand splints and arm braces, and on functional assistive hand splints, feeding devices, special assistive devices of many varieties such as swivel spoons, comb-and razor-holders and page turners for use on a T-bar, et cetera. This book is of value to orthopedic residents, surgeons, orthotists, prosthetists, occupational therapists, physical therapists, physiatrists, and rehabilitation specialists. As all are members of any well organized rehabilitative team for the care of disabled patients; they should all understand their place in the program and the importance and relationship of their work to that of all the other members of the team. Such understanding will automatically result when any intelligent person reads this book. Highly recommended for all. —*DAVID C. KELLSEY, Lt. Col., USAF (MC)*

ROENTGENOLOGY OF THE CHEST, edited by *Coleman B. Rabin,* M. D., F. C. C. P. 484 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $19.50.

The stated purpose of this book is to present roentgenology of the chest to the radiologist from the clinical standpoint, and to the clinician from the radiologist's viewpoint. This bilateral approach to the problem of disease of the heart and lungs is unique and the end result is excellent. The separate chapters of physiology, anatomy and surgery are written by leading experts on their own specialties. An outstanding example of this bilateral approach is the chapter on "Special Signs in Roentgenology." This will aid the clinician in understanding the specific meaning of shadows on the chest x-ray. Understanding these

signs aids the evaluation of chest films and is the difference between intelligent interpretation of the roentgenograms and pure guesswork which depends upon a good memory of previous case material. On the other hand, for the radiologist there is a chapter on physiologic considerations of intra-alveolar pressure. This type of information will improve his ability to get the maximum information obtainable from a chest film. All of the major and many of the rare chest diseases are very adequately covered. This is considered to be the most complete, yet concise, highly readable textbook on chest disease available. It would be a most valuable addition to the library of anyone involved with chest disease or chest roentgenology.

—JAMES M. KEEGAN, Lt. Col., USAF (MC)

DISEASES OF THE ESOPHAGUS, by *J. Terracol* and *Richard H. Sweet.* 682 pages; illustrated. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $20.

This is the first American edition of a book which appeared originally in French for the first two editions. This is an ideal volume for all physicians interested in the diseases of the esophagus. The sections on anatomy, physiology, and normal roentgen examination of the esophagus are outstanding. The operative procedures are explained in great detail. The indications and contraindications for esophagoscopy and other instrumental exploration are covered completely. The organization of the various afflictions of the esophagus by chapters makes this a ready reference book with information easily available. Every condition that might occur to or in the esophagus is covered completely. The appendix contains diets and tube feedings for patients with esophageal diseases. The bibliography for the second French edition is included in its entirety but the bibliography for the first edition is not included. The majority of the references are in foreign literature, but the material pertaining to recent advances in the treatment and diagnosis of diseases of the esophagus in the American literature is included. All of the illustrations are clear and more than adequate for a complete understanding of the condition discussed. This book is recommended for the library of all military hospitals and also for any physician who is interested in diseases of the esophagus, whether from a surgical or internal medical standpoint. The operative descriptions would be very valuable to the chest surgeons.

—EDWARD P. McLARNEY, MC, USN

ADVANCES IN INTERNAL MEDICINE, edited by *William Dock,* M. D., and *I. Snapper,* M. D. Volume IX. 311 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1958. Price $8.50.

The editors of this annual volume each year select eight to ten topics of importance in internal medicine for review. The subjects cover areas of general interest wherein recent advances have made an up-to-date review of particular value. Each section is written by a recognized authority in that field. The areas covered this year are vitamin B_{12} metabolism, corticosteroids and infections, hyperparathyroidism, hereditary defects in clotting mechanisms, pathogenesis

of glomerulonephritis, pathophysiology of carcinoid tumors, and renal tubular function. The discussions are well and carefully written, include numerous references, and give a clear, concise summary of the background and current status in that field. The volume has an author and subject index which adds to its value. The indexing and extensive bibliography make it a valuable source of references to other articles in the literature. It is highly recommended.

—*CHRISTIAN GRONBECK, Jr., Lt. Col., MC, USA*

A MANUAL ON CARDIAC RESUSCITATION, by *Robert M. Hosler,* M. D., F. A. C. S. 2d edition. 208 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $5.50.

This is the second edition of a well-written manual. The value of proper management of cardiac arrest is stressed throughout, and responsibility to meet this emergency is placed squarely on the shoulders of every physician who attempts surgery. Much research and thought has gone into the compilation of this manual. Application of cardiac resuscitation has been extended beyond the surgeon and operating room; indications for thoracotomy and cardiac massage are broadened. Dr. Hosler suggests and proves that at times our conception of death is reversible. He cites the work of Yater, who found in 950 autopsies of men who died of coronary artery disease that one third showed no evidence of myocardial damage. This suggests that many of these cases might have seen saved if cardiac resuscitation had been available. The case of a doctor so resuscitated is cited. Recognition and treatment of cardiac arrest with or without ventricular fibrillation are carefully outlined. Stress is placed on re-establishment of the oxygen system, and restoration of the heart beat. Every required instrument and drug is described. The technic of massage and many of the instruments are illustrated by photograph or drawing. The contents of this book should be known to all anesthesiologists and to all surgeons regardless of subspecialty. It should be in the library of all hospitals and a part of the resuscitation kit of all emergency and operating rooms. The material also should be taught in every medical school.—*LUTHER G. BELL, Capt., MC, USN*

A THERAPY FOR ANXIETY TENSION REACTIONS, by *Gerhard B. Haugen,* M. D.; *Henry H. Dixon,* M. D.; and *Herman A. Dickel,* M. D. 110 pages. The Macmillan Co., New York, N. Y., 1958. Price $3.50.

Over twenty years ago Edmund Jacobson, at the University of Chicago, described a controversial type of therapy for treating chronic anxiety tension states. In this monograph, written by three psychiatrists from the University of Oregon for nonpsychiatric physicians, a modification or short cut to the Jacobson method is described. The basis of this thesis is that tension is a habit. The chronically tensed person has practiced tensing largely by imitation, and the tension has been habit forming. Muscle tension comes first, anxiety follows as a part of general homeostasis. The habit can be changed like any other habit. Anxiety will persist as long as tension is present. This book describes the method of changing the habit of tension. First the patient learns

the purpose and goal of relaxation. Then he has experiments to do. He sits comfortably in an armchair, rests forearm on arm of chair, has hand hanging over front of chair. He raises hand, tenses muscles, suddenly lets hand drop. He studies hand in order to consciously experience feeling of relaxation. This is done four or five times daily for 10 to 15 minutes, then other groups of muscles are tackled until the entire body is relaxed. It may take six months to reach the goal, which is for the patient to be relaxed not only in ordinary situations but also under stress. The book monograph gives a good description of primary and secondary symptoms of tension reaction. It also describes the most common tools a therapist has in treating tension. Three complete case histories are given. The interviews with the patient and directions and advice are treated adequately in these three cases. The three authors state that this form of therapy is to be used for the chronically tensed person, the person who ordinarily would receive sedation. It is not to be used on psychopaths, mental defectives, psychotics, or in emergency anxiety state.

—*FRANCES L. WILLOUGHBY, Capt., MC, USN*

ABDOMINAL OPERATIONS BY THE VAGINAL ROUTE, by *Paul Werner,* M. D., and *Julius Sederl,* M. D. Translated by *L. M. Szamek,* M. D., with a Foreword by *Richard W. TeLinde,* M. D. 165 pages; 120 plates. J. B. Lippincott Co., Philadelphia, Pa., 1958. Price $9.

This book is well illustrated and emphasizes how technics of the vaginal approach possess many advantages over laparotomy. It is a complete, precise, and clear presentation of pelvic operations that can be performed by the vaginal route. Actually the title is a misnomer inasmuch as these procedures are pelvic operations rather than purely abdominal. The text has obviously been written by experts in this technic. As Dr. TeLinde has stated, difficulties in performance of such procedures do not constitute a legitimate excuse to avoid doing them, particularly if they are at a distinct advantage to the patient. This subject is obviously controversial and advocates on either side of the issue can readily be found. Every gynecologist should be familiar with the contents of the volume, and should honestly reappraise his thinking and his own technics in the performance of these procedures by the vaginal route. The authors point out that the technics displayed are not as difficult to acquire as some people imagine. The text is an excellent addition to the library of any physician interested in gynecologic technics.

—*HUMBERT L. RIVA, Col., MC, USA*

CHRONIC SCHIZOPHRENIA, by *Thomas Freeman,* M. D., D. P. M.; *John L. Cameron,* M. B., CH. B., D. P. M.; and *Andrew McGhie,* M. A. Preface by *Anna Freud.* Foreword by *T. Ferguson Rodger.* 158 pages. International Universities Press, Inc., New York, N. Y., 1958. Price $4.

Chronic Schizophrenia is a unique book in that it combines the talents of an analytically oriented psychiatrist, a clinical psychologist, and a psychologist interested in research in a two-year study of chronic deteriorated schizophrenics. The authors utilized three interrelated methods in their study consisting of group psychotherapy, modified

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milieu therapy, and daily direct observations by the individual authors of patients on a female refractory ward.

The authors note that the ability to differentiate the self from the environment is damaged in schizophrenia and that this is the basic disturbance. The other schizophrenic manifestations are considered to be necessary elaborations of it. This breakdown of ego boundaries results in the patient's confusion of his personal identity, and the writers devote a major portion of the book presenting interesting examples with discussion and interpretations in support of the basic concept.

Two chapters are devoted to the theory of mental functioning with a chronologic development of the various psychopathologic theories of schizophrenia. There is an excellent chapter on the treatment of chronic schizophrenia in a therapeutic environment, followed by a chapter of general conclusion to make a fitting ending to this book.

In my opinion, the authors are to be congratulated for an excellent study of a heretofore much neglected group of patients. This work should be of interest and value to psychiatrists and related workers who are interested in the analytic study of mental illness. Others also should find it of value because it provides a clear picture of the thinking process of chronic schizophrenics. I can't help but think that this work may be one of the last studies of chronic schizophrenia from the analytically oriented viewpoint, because the current influence of tranquilizers with the emphasis on the chemophysiologic aspects of psychoses will probably dominate the trend of investigational studies for many years to come.

This book deserves a place in any well-rounded library on psychoses.

—*STEPHEN MOURAT, Lt. Col., MC, USA*

MEDICAL EMERGENCIES, Diagnosis and Treatment, by *Francis D. Murphy*, M. D., F. A. C. P., and Associate Authors. Foreword by *George Morris Piersol*, M. D. 6th edition. 635 pages; illustrated. F. A. Davis Company, Philadelphia, Pa., 1958.

This is the sixth edition of a well-known, practical book on the diagnosis and treatment of medical emergencies. Major revisions have been made in chapters dealing with the collagen diseases, acute renal failure, liver diseases, and antibiotic therapy of acute infections. The most recent trends in the treatment and prevention of rheumatic fever are succinctly presented. However, not all regimens for the treatment of other collagen diseases are given.

Though a clear and comprehensive table of the differential diagnosis of acute glomerulonephritis and acute toxic nephrosis (lower nephron nephrosis or acute renal failure) is given, certain details of treatment presented are either controversial (*e. g.*, three days of serum albumin given intravenously for the former) or not clearly spelled out (*e. g.*, types and quantity ranges of parenteral fluid recommended for the latter).

Occasionally, the primary aim of conciseness is somewhat impaired by inclusion of diseases that are not strictly emergencies (*e. g.*, certain chronic anemias). In other places reference to certain theories is made. Interesting as these may be, it is believed that at least some of the space devoted to them could profitably be devoted to more detail on appropriate topics.

The revised section on diseases of the liver is superb for its concise, yet comprehensive account of the pathophysiology, differential diagnosis, precise interpretation of laboratory tests, and illustrations of physical examination technics, as well as treatment.

The appendix on chemotherapy of the common bacterial infections furnishes a practical and ready reference to drugs for certain bacteria and their efficacy according to recently compiled percentages. This permits the best selection before results of sensitivity tests are available.

This volume is heartily recommended to medical students, interns, residents, and general practitioners.

—*H. LEONARD JONES, Jr., Capt., MC, USN*

THE BRAIN AND HUMAN BEHAVIOR, Proceedings of the Association for Research In Nervous and Mental Disease, December 7 and 8, 1956, New York, N. Y. Editors: *Harry C. Solomon*, M. D.; *Stanley Cobb*, M. D.; and *Wilder Penfield*, M. D. 564 pages; with 200 illustrations and 53 tables. The Williams & Wilkins Co., Baltimore, Md., 1958. Price $15.

This is the thirty-sixth in a series of annual symposia, each devoted to a subject of current interest. The current topic is discussed by an imposing group of neurologists, psychiatrists, neurophysiologists, pharmacologists, chemists, anatomists, psychologists, and neurosurgeons. Like many of its predecessors the book is well bound, clearly printed, expensive, and dull. An avalanche of words effectively reduces reader interest. This reviewer searched for clear, simply expressed ideas, but found few. The best papers are short, but unfortunately few in number. This reviewer found the book hard to finish. No real definition of "The Brain and Human Behavior" appeared. Much speculation, free association, and philosophical meandering obscure what facts are available. An index of sorts plus a list of the association's membership completes the book. It is too expensive and too long for any but those with an excess of time and a lively interest in this important topic to enjoy.—*HENRY W. HOGAN, Maj., MC, USA*

CLINICAL OBSTETRICS AND GYNECOLOGY, Volume 1, Number 1. A quarterly book series. Symposium on Medical Problems in Pregnancy edited by *Curtis J. Lund*, M. D. Symposium on Management of Endocrine Problems edited by *Allan C. Barnes*, M. D. 288 pages; illustrated. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, N. Y., March 1958. Price $18 for four consecutive numbers.

The section on medical problems in pregnancy was not intended to replace the works of other specialists, but to present the point of view of specialists on the common medical complications, so important in

the morbidity and mortality of pregnancy. In the first chapter on anemia in pregnancy, a brief history of the advance of this problem in obstetrics, plus a classification of anemia in pregnancy and its treatment, is given. This subject is then concluded with an excellent summary on the factors introduced by pregnancy, which singly or in combination produce anemia. A word of caution about whole blood transfusion as not being the treatment of choice for any common pregnancy anemia is an important one. In addition, prevention is a duty of the physician to his patient. The section on management of endocrine problems begins with diagnostic aids for endocrine management. The fact is emphasized that none of the various forms of therapy ranging from diet to various hormones has stood the test of time in the treatment of dysfunctional uterine bleeding. Most important is proper diagnosis and intermittent progesterone therapy. The Menopause, by Dr. Barnes, emphasizes the need for accurate rather than casual diagnosis, with the need for actual laboratory procedures being necessary only in the case of possible premature menopause occurring in the thirties or earlier. Other sections of the text deal with the endocrine treatment of sterility, followed by threatened and habitual abortion, management of diabetes and pregnancy, problems related to growth and sexual development, the adrenogenital syndrome and adrenal hyperplasia, and precocious and delayed sexual development. This text is a concise review of the previously stated problems with an up-to-date bibliography of each subject. It is of definite interest and value to the specialist in these fields.

—HUMBERT L. RIVA, Col., MC, USA

THE MANAGEMENT OF CHILDHOOD ASTHMA, by *Frederic Speer*, M. D. 116 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $4.75.

This is an excellent, concise book on a disease important to the general practitioner and the pediatrician. The author has condensed his presentation, but adequately covered his subject.

Treatment of childhood asthma varies regionally according to local problems such as climate, allergens, et cetera. While the author has undoubtedly been influenced by his experiences in Kansas, most of his suggestions are applicable throughout the country. Little is said about the psychic factors in aggravating the disease. His emphasis upon a careful history and the establishment of good rapport with the parents is especially to be commended. This is a practical and authoritative book and is a welcome addition to the medical literature on this subject.—*JOHN F. SHAUL, Capt., MC, USN*

ANOMALIES OF INFANTS AND CHILDREN, by *D. McCullagh Mayer*, D. D. S., M. D., F. A. C. S., F. I. C. S., and *Wilson A. Swanker*, M. D., F. A. C. S., F. I. C. S. 454 pages; illustrated. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, N. Y., 1958. Price $12.

This book is just what it is stated to be, "written primarily for the student and general practitioner." As such, it does an extremely fine job of covering congenital and acquired anomalies of children from a general point of view. The contents are subdivided into specific areas

for easy reference, and the index is good for easy location of specific anomalies, both of which make for ready access to the user.

The various entities are broken down and discussed as to definition, etiology, diagnosis, prognosis and treatment. The embryology sections are good for this type of book but the treatment sections could be a bit more specific in certain cases. The etiology section would be excellent for the parents of deformed children to read as explanations for their many doubts and questions. Two or three of the classifications of anomalies in this book are new and not in keeping with those of general usage. I do not believe that further confusion of the medical nomenclature is indicated.

This book is excellent for the medical student, intern, and young resident in many of the specialties, and can serve as a ready reference book for a quick "bird's-eye view" of a specific entity in this field. The last chapter, "Accidents to Children," should be read and absorbed by everyone. It is a giant step in the right direction, that of preventive medicine, to which we all should pay more attention.

—*HAL B. JENNINGS, Jr., Lt. Col., MC, USA*

ELECTROCARDIOGRAM CLINICS, by *Joseph E. F. Riseman,* M. D., and *Elliot L. Sagall,* M. D. Clinic I: The Diagnosis and Treatment of Angina Pectoris; Clinic II: The Role of the Electrocardiogram in Establishing the Diagnosis of Acute Myocardial Infarction; Clinic III: Problems in the Diagnosis of Acute Myocardial Infarction; Clinic IV: The Role of the Electrocardiogram in the Diagnosis of Pulmonary Embolism. 259 pages; illustrated. The Macmillan Company, New York, N. Y., 1958. Price $10.50.

This book covers only one small aspect of electrocardiography. It deals with the electrocardiographic tracings found in patients with coronary artery disease, angina pectoris, and myocardial infarction. The text is a series of electrocardiograms of patients, with clinical history and physical findings and other pertinent clinical data. After a brief presentation of the clinical aspects, the electrocardiogram is interpreted and the case is discussed in a question and answer manner. While the concept of presenting electrocardiogram clinics is good, it is unfortunate that the authors have restricted their interpretations to old style pattern terminology. Each electrocardiogram is interpreted by groups of leads beginning with the standard lead, the augmented limb leads and finally the unipolar precordial leads. After this descriptive terminology, the final interpretation is made. Most interpretations of each electrocardiogram occupy a full printed page. One wonders if the authors are familiar with the relationship of the augmented limb leads to the bipolar standard leads and the use of modern vector concepts. The reader who is interested in concise, modern electrocardiographic principles will not find them in this text. It is open to criticism on a number of the clinical interpretations and inferences which are made, and presents no new facets in the field of electrocardiography.—*LAWRENCE E. LAMB, M. D.*

A TEXTBOOK OF ORAL PATHOLOGY, by *William G. Shafer,* B. S., D. D. S., M. S.; *Maynard K. Hine;* D. D. S., M. S.; and *Barnet M. Levy,* A. B., D. D. S., M. S. 714 pages; illustrated. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $15.

The most marked favorable feature of this text is the clarity of presentation of material. Each subject and lesion is discussed in terms of its clinical features, histologic features, and treatment and prognosis. Of great value as a teaching text for undergraduate dental students, is the thorough and modern coverage given to dental caries, diseases of the pulp and periapical tissues, and periodontal disease. These areas represent the bulk of the problems facing the average general practicing dentist. A few specific criticisms are worthy of note. In the discussion of fissural or developmental cysts, no mention is made of the median mandibular cysts. The problem of the oral keratoses and the need for separation from leukoplakia is well discussed. However, the illustrations offered are so small that the important feature of dyskeratosis cannot be visualized. This seems to detract from the value of such a discussion. It appears to be of questionable value to include the radicular cyst with the odontogenic tumors; notwithstanding the author's introductory statement concerning involvement of similar tissues. Traditionally, and on a basis of clarity, continuity is better established by inclusion with periapical lesions. This text is highly recommended for use in teaching oral pathology to dental students, to dental specialists, and to general practitioners of dentistry who desire a firm foundation in oral pathology.

—*WILLIAM G. SPRAGUE, Maj., USAF (DC)*

CLINICAL PERIODONTOLOGY, The Periodontium in Health and Disease (Recognition, diagnosis and treatment of periodontal disease in the practice of general dentistry), by *Irving Glickman,* B. S., D. M. D., F. A. C. D. 2d edition. 978 pages; illustrated with 720 figures. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $17.50.

The appearance of a new edition makes us wonder what changes have justified it. In this second edition, the whole book has been reworked, and there are changes. Greatest of these is the addition of the section on gingival plastic surgery following current philosophies of practice. Some bibliographies have been condensed; however, all classic references are retained. There has been some rearranging of subject material into more homogeneous groupings and changes in sequence. The printing and format are different. The illustrations are clearer and more detailed. To those of us who have become attached to the first edition this is an improvement, but not an obsolescence, of what is probably the most comprehensive periodontal text in the English language. The author's wide experience in research, teaching, and as a practicing clinician makes the book of universal appeal to students, general practitioners, and specialists in periodontia.

Half of the book is devoted to a clear definitive treatment of practical applications. The balance treats periodontal anatomy, histology, physiology, pathology, etiology, and classification. There is thorough cover-

age of each subject. For those interested in improving the general standards of practice, here is a book which can almost be guaranteed to do so. For the uninitiated it will certainly open fascinating possibilities for successful treatment.—*JULES D. KARTMAN, Lt. Col., USAF (MC)*

PRINCIPLES OF RESEARCH IN BIOLOGY AND MEDICINE, by *Dwight J. Ingle,* B. S., M. S., Ph. D. 123 pages. J. B. Lippincott Company, Philadelphia, Pa., 1958. Price $4.75.

This small volume consists of the author's views on those problems in research which relate primarily to the philosophy of work as it is commonly undertaken in the clinical and laboratory approach to medical problems. He has cleverly introduced the humor of Lewis Carroll to emphasize some of his principles.

The eleven chapters cover such general subjects as limitations of mind, causality, probability, heteropoietic factors, interpretation of results, and therory in biology and medicine. Each of these is in itself so complex that volumes have been written on them. The author's coverage of the subject is limited to principles, but is sometimes lost because of the lack of specific examples to illustrate what the author considers important points.

For those engaged in medical research, the volume will provide an interesting evening's entertainment.

—*JAMES B. HARTGERING, Lt. Col., MC, USA*

ELECTROCARDIOGRAPHIC ANALYSIS, Volume I, Biophysical Principles of Electrocardiography, by *Robert H. Bayley,* M. D. 237 pages; illustrated. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, N. Y., 1958. Price $8.

This authoritative book by a noted electrocardiologist is the first of a series. Lest readers be awed by the title of this volume, its forthcoming companion, *Clinical Aspects of Electrocardiography,* will hold more promise for the physician who is oriented toward purely clinical aspects of the subject. Because the analytic method of presentation employed by the author is developed in a stepwise manner, the reader must resist the strong temptation to hurry through the tedious study required to gain an understanding of concepts relating to the solid angle, membrane potentials, and double layer distribution, because these discussions among others formulate the basis for consideration of the more appealing clinical subjects which follow. It is difficult to single out any one section of this treatise for special comment. It is the over-all integration of the concepts presented which will provide the reader with a rational approach to an analysis of unusual electrocardiograms or difficult problems which do not fit a "recognized pattern." It is appropriate to indicate, however, that the sections devoted to the abnormalities of vector accession (depolarization) are excellent, particularly with respect to the relationship of myocardial infarction and conduction disturbances. One of the most valuable features of this book may be found in the chapters dealing with T-wave abnormalities, the ventricular gradient, and the current of injury, be-

cause much of the material offered concerning these subjects cannot be readily found elsewhere. The sections on local ventricular ischemia including the electrocardiographic changes of impending myocardial infarction are of particular interest. A comprehensive chapter on mathematical considerations is available for those interested in this phase of the subject and the more uninitiated will find the glossary of frequently used terms of considerable assistance. This book was written for the "serious students of the subject." Those who are unwilling to devote the time and effort required to master the basic concepts, which are difficult to grasp, will find themselves hopelessly lost. On the other hand, those diligent readers who persevere and accomplish an understanding of the fundamentals will be rewarded. To this group the book can be highly recommended.

—*JAMES A. ORBISON, Lt. Col., MC, USA*

DISCOVERING OURSELVES, A View of the Human Mind and How It Works, by *Edward A. Strecker,* M. D., Sc. D., and *Kenneth E. Appel,* M. D., Sc. D., in collaboration with *John W. Appel,* M. D. 3d edition. 303 pages; illustrated. The Macmillan Company, New York, N. Y., 1958. Price $4.75.

This primer of dynamic psychology needs no introduction. Three editions and many thousands of copies over a period of 27 years attest both to its value and its success. Written by two of this country's foremost psychiatrists it manages in simple and lucid style to succeed where many more ponderous and highly technical tomes fail, namely, in imparting most of the basic and acceptable principles of dynamic psychiatry in simple English. The great need today in imparting information to others is the ability to communicate. This primer does this admirably and can be understood and enjoyed at all educational levels. It is particularly recommended to the layman, the novice in psychiatry and the ancillary services, and especially to the so-called well-trained individual who has forgotten to converse in "plain English," or who is called upon to train groups not so educationally fortunate as himself.—*RICHARD R. CAMERON, Col., MC, USA*

PROGRESS IN PSYCHOTHERAPY, Volume III, Techniques of Psychotherapy, edited by *Jules H. Masserman,* M. D., and *J. L. Moreno,* M. D. 324 pages; illustrated. Grune and Stratton, Inc., New York, N. Y., 1958. Price $8.50.

This volume, one of a series issued yearly, deals with current concepts of dynamically oriented psychotherapy and the various technics used. The editors have done an excellent job of selecting extremely good articles, written for the most part by outstanding people familiar with each technic. A small portion of the book deals with historical development in psychotherapy, and is followed by a large section dealing with rationale and methods, and containing some fascinating and thought provoking analogies. The authors do not spare feelings in dissecting some of the established scientific "truths," and revealing that their basic principles are at times far from flawless and often mutually excluding.

A sizeable section is devoted to special technics and contains articles dealing with such a variety of subjects as military psychiatry, marriage counseling, the use of projective tests in psychotherapy, et cetera. A pertinent portion of the book deals with psychopharmacology and calls to attention the rather sobering deficiencies of our knowledge of pharmacodynamics, as it relates to biochemistry and neurophysiology. Such knowledge is imperative for the adequate understanding of the behavioral effects of drugs in man.

The book is concluded with some "newsy" reports of psychotherapy with specific problems as experienced in Canada, Greece, Latin American countries, et cetera. The book is well worth reading, especially for those who have completed or are far advanced in their psychiatric training. Although one may not agree with some of the ideas expressed by the over forty authors, one must admit that there is no lack of thought-provoking comments.

—*STEPHEN MOURAT, Lt. Col., MC, USA*

COCCIDIOIDOMYCOSIS, by *Marshall J. Fiese,* M. D., F. A. C. P. Foreword by *Charles E. Smith,* M. D. 253 pages; illustrated. Charles C Thomas, Springfield, Ill., 1958. Price $9.50.

Until about 20 years ago coccidiocidal disease was of intimate concern only to physicians of sparsely settled endemic areas in California, Arizona, New Mexico, Texas, Mexico, and Argentina, who had the responsibility of treating patients with the disease. Now, however, nearly 700,000 acres of San Joaquin Valley land in California have been put under cultivation, many thousands of acres of the Sonora Desert in Arizona have been turned into farms, thousands of people have migrated into the farm lands of Central California, and each year several million nonimmune people travel in and through these endemic areas, some to develop symptoms after returning home. The infection has become of increasing interest to medical workers in all parts of the country, and other parts of the world, and it will become even more so. This scholarly monograph, summarizing work done during the past 50 years and especially during the last two fruitful decades, is most timely. Its content is of value to specialists in many fields because it deals competently with the history, epidemiology, mycology, geographic distribution, immunology, pathogenesis, clinical course, prevention and treatment of a disease which, fortunately usually mild and self-limiting, can in its disseminated forms be most disfiguring and highly lethal; it can also play havoc in a laboratory where the fungus is not recognized as a constant danger and where due precautions therefore are not observed. Once begun, the book is put aside only with difficulty until it has been read through. Research workers will find the bibliography of 968 references most helpful. As stated by Charles E. Smith, M. D., in the foreword, the monograph should be a major factor in making succeeding decades even more productive than the last two. The areas in which more knowledge is needed are indicated clearly.

—*SIDNEY A. BRITTEN, Capt., MC, USN*

MOULD FUNGI AND BRONCHIAL ASTHMA, A Mycological and Clinical Study, by *P. J. Van Der Werff.* Volume I. With a foreword by Prof. Dr. *Johanna Westerdijk.* 213 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $7.50.

The book by the head of the Amsterdam Clinic for allergic diseases is the first of a three-volume study of the general, ecologic and sociologic aspects of mycology, including extensive investigations, in the Netherlands. Later volumes will deal with the problem of the clinical significance of various airborne mould spores in the Netherlands and with the clinical significance of mould fungi growing in the respiratory tract. Data of the occurrence of spores and moulds in the atmosphere, either in houses or factories as well as in the open air, in the Netherlands should be of much interest to investigators in this country. An excellent chapter on laboratory methods calls attention to faulty collection technics to explain divergent findings of other investigators. The volume contains an unusually extensive bibliography of more than four hundred titles from the world literature on this subject. Excellent microphotographs of the mould fungi encountered will prove helpful to the student of mycology.

—*C. B. WHITE, Col., USAF (MC)*

PSYCHIATRIC RESEARCH REPORTS OF THE AMERICAN PSYCHIATRIC ASSOCIATION, edited by *Members of the Committee on Research,* 1956-57: *Nathan S. Kline,* M. D.; Chairman; *Robert A. Cleghorn,* M. D.; *Milton Greenblatt,* M. D.; *Harold E. Himwich,* M. D.; *William T. Lhamon,* M. D.; *Benjamin Pasamanick,* M. D. No. 9. "Research in Psychiatry with Special Reference to Drug Therapy." Papers presented at the Regional Research Conference held under the joint auspices of the American Psychiatric Association and the Medical Schools and Affiliated Hospitals of Philadelphia, Pa., 16-17 Nov. 1956. 181 pages; illustrated. American Psychiatric Association, Washington, D. C., 1958. Price $2.

This is an excellent addition to a series which was begun in July 1955 under the auspices of the American Psychiatric Association, and contains papers presented at a conference in Philadelphia in November 1956. A portion is devoted to studies of proclorperazine, and there is an excellent discussion and critique on methodology of research in psychiatry. The reader is quickly made aware of the numerous problems encountered in establishing working procedures, criteria, and acceptable standards of reference in studying the effects of drug therapy. The relative potency of the milieu, for one example, must be taken into full account and conclusions based on findings with animals cannot be easily transposed and used as parallels to human beings. It is pointed out that extreme care must be exercised in use of such terms as "anxiety" and "catatonia" as observed in animals when we actually are using them in a strictly descriptive sense. I was particularly pleased at the realistic attitude of some of the commentators in emphasizing that clinically the changes produced or brought about by the use of tranquilizers were quantitative diminutions of the symptoms and not a qualitative alteration of the schizophrenic process. This is a reference worth having and at a modest price.

—*STEPHEN MOURAT, Lt. Col., MC, USA*

ELECTRONIC INSTRUMENTATION FOR THE BEHAVIORAL SCIENCES, by *Clinton C. Brown,* Ph. D., and *Rayford T. Saucer,* Ph. D. A Monograph in The Bannerstone Division of American Lectures in Objective Psychiatry, edited by *W. Horsley Gantt,* M. D. 160 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $5.50.

This monograph includes an introduction to the basis of electronics, reviews the vacuum tube theory, discusses power supplies, amplifiers, oscillators, and timing circuits. Stimulus generators and the variety of input transducers for handling these stimuli are the subject of another chapter. The chapter on test instruments reviews the principles of operation of the commonly used laboratory instruments. Another is devoted to details of setting up a laboratory, sources of equipment are suggested. There is a chapter devoted to the theory and application of transistors. A sizeable list of references is included for the reader who wishes to delve deeper. Many diagrams and illustrations are used to clarify the text. Investigators in experimental psychiatry and related fields will find this a useful reference manual.

—*ROBERT L. WILLIAMS, Lt. Col., USAF (MC)*

CIBA FOUNDATION SYMPOSIUM ON THE CEREBROSPINAL FLUID—Production, Circulation and Absorption. Editors for the Ciba Foundation: *G. E. W. Wolstenholme,* O. B. E., M. A., M. B., B. Ch., and *Cecilia M. O'Connor,* B. Sc. 335 pages; 141 illustrations. Little, Brown and Company, Boston, Mass., 1958. Price $9.

Among the many questions considered at this symposium were: How accurate is our information about the anatomy of the pia-arachnoid, of the arachnoid villi, of the choroid plexuses, of the innervation and vascularization of these structures, and of the arrangement and significance of the subarachnoid, perivascular, and perineuronal spaces? Do we really know where, how, and why the cerebrospinal fluid is produced and absorbed, and is it a secretion, excretion, or transudate? Is the process under nervous or hormonal control, are there secretory granules in the choroidal epithelium, and what is the true function of the choroid plexuses? Can we explain the blood-brain and blood-cerebrospinal fluid barriers and their variations at different ages and in different regions? By what means and for what reason does the cerebrospinal fluid circulate? And how may all these fundamental considerations be correlated with clinicopathologic observations or utilized to determine the most rational modes of treatment? Anatomists, neurologists, pathologists, psychiatrists, pharmacologists, and neurosurgeons came from all parts of the world to attend this meeting to contribute from their research and reflections. The book contains 15 papers presenting careful and commendable work on the structure and function of choroid plexuses, arachnoid-granulations, and meninges; on the formation, circulation, and absorption of cerebrospinal fluid; and on blood-cerebrospinal fluid-brain barriers. The open discussions following each paper are very interesting, especially the concluding one. This volume is recommended for purchase by medical libraries but not by individuals.

—*THEODORE M. BADGLEY, Maj., MC, USA*

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, Vol. 70, Art. 3, pages 277-762, June 3, 1958. Editor in chief, *Otto V. St. Whitelock.* "Animal Disease and Human Health," a monograph based on papers presented at a conference held by the Academy in collaboration with the Communicable Disease Center, Public Health Service, Atlanta, Ga., 11-13 September 1957. Conference Chairman and Consulting Editor: *James Lieberman.* 485 pages; illustrated. The New York Academy of Sciences, New York, N. Y., 1958.

The physician, the doctor of veterinary medicine, and allied scientists will find much of interest in this monograph, which represents over 10 years of technological progress since publication in 1947 of the proceedings of the initial meeting. The subjects presented and varied disciplines represented by the contributors serve to highlight the complexities and infinite variety of relationships that exist between animal diseases and human health. All aspects of human and veterinary medicine are covered. Contributors stem from every element of world health services. In essence the monograph serves to emphasize the need for an integrated multidiscipline approach in problem areas. This publication is organized in eight parts with a comprehensive introduction and summary. Bibliographies are extensive and the subject material well supported by the use of graphs, charts, and photographs. As stated in the excellent summary, which gives a synopsis of the conference: "No one discipline can provide the technical prowess necessary for the solution of problems of such complex ecology; this has been made abundantly clear throughout this publication. Furthermore, no one discipline can afford the luxury of neglecting to seek the aid of others. Animal and human health problems reside within the same continuum; they cannot be removed and studied as isolates."

—ROBERT R. MILLER, Col., USAF (VC)

THE YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY (1957-1958 Year Book Series), edited by *William B. Wartman,* B. S., M. D. 478 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1958. Price $8.

This annual publication maintains its usual high standards in reviewing the significant literature of pathology and clinical pathology for the past year in abstract form. The editor has not only made a careful selection of articles but has added his own comments, interpreting and correlating the material, so that the reader obtains a broader viewpoint of the subject matter. Particularly valuable is the rather extensive coverage of the foreign literature. An interesting feature is the excerpts from the editor's diary of his six-month tour of Europe. As he states, he visited many clinics to broaden his outlook and improve his thinking. It makes one think that perhaps more of us should do the same. The book follows the traditional format, taking up first general, then systemic pathology, and finally clinical pathology. It is well bound, easily read, and the illustrations are well reproduced. The volume may be considered essential for every pathologist and resident in pathology. *—HOWARD A. VAN AUKEN, Col., MC, USA*

New Books Received

Books received by the *U. S. Armed Forces Medical Journal* are acknowledged in this department. Those of greatest interest will be selected for review in a later issue.

COLD INJURY, GROUND TYPE, Medical Department United States Army in World War II, by Colonel *Tom F. Whayne,* MC, USA (Ret.), and *Michael E. DeBakey,* M. D. Prepared under the direction of Major General *S. B. Hays,* MC, USA. Editor in Chief: Colonel *John Boyd Coates, Jr.,* MC, USA, Associate Editor: *Elizabeth M. McFetridge,* M. A. 570 pages; illustrated. U. S. Government Printing Office, Washington, D. C., 1958. Price $6.25.

RADIATION PROTECTION, by *Carl B. Braestrup* and *Harold O. Wyckoff.* Contributors: *Merrill Eisenbud, Titus C. Evans,* and *S. Allan Lough.* 361 pages· illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $10.50.

SOCIAL PSYCHIATRY IN ACTION, A Therapeutic Community, by *Harry A. Wilmer,* Ph. D. Foreword by *Francis J. Braceland,* M. D. Preface by Rear Admiral *Bartholomew W. Hogan,* MC, USN. 373 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $8.75.

REHABILITATION IN INDUSTRY, edited by *Donald A. Covalt,* M. D., with a foreword by *Howard A. Rusk.* Eleven contributors. Modern Monographs in Industrial Medicine. Editor in Chief: *Anthony J. Lanza,* M. D. Consulting Editor: *Richard H. Orr,* M. D. 154 pages; illustrated. Grune & Stratton, Inc., New York, N. Y., 1958. Price $6.

ADVANCES IN PEDIATRICS, Volume X. Editor: *S. Z. Levine.* Associate Editors: *John A. Anderson, Margaret Dann, A. Ashley Weech, Myron E. Wegman,* and *Warren E. Wheeler.* 362 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1958. Price $9.

TRANSPORTATION OF THE INJURED, Emergency Procedures for Ambulance Crews, Training, Equipment, Vehicles, and Responsibility for Ambulance Service, by *Carl B. Young, Jr.,* M. P. H. Collaborating physician: *Carl B. Young,* M. D., F. A. C. S. Drawings by *Richard Fry, Jr.,* B. S. 238 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $6.75.

PHYSICAL EXAMINATION OF THE SURGICAL PATIENT, by *J. Englebert Dunphy,* M. D., F. A. C. S., and *Thomas W. Botsford,* M. D., F. A. C. S. 2d edition. 375 pages; illustrated. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $8.

THE EXCITABLE CORTEX IN CONSCIOUS MAN, by *Wilder Penfield,* O. M., C. M. G., Litt. B., M. D., D. Sc., F. R. C. S., Hon. F. R. C. P., F. R. S. The Sherrington Lectures, V. 42 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $2.50.

SHERRINGTON, Physiologist, Philosopher and Poet, by The Right Honourable Lord *Cohen* of Birkenhead, M.D., D. Sc., LL. D. F. R. C. P., F. A. C. P., F. F. R., F. S. A., J. P. The Sherrington Lectures, IV. 108 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $3.50.

A CLASSIFIED BIBLIOGRAPHY OF GERONTOLOGY AND GERIATRICS, Supplement 1, 1949-1955, by *Nathan W. Shock.* 525 pages. Published under a grant from the Forest Park Foundation, Peoria, Ill. Stanford University Press, Stanford, Calif., 1957. Price $15.

THE NEUROLOGICAL EXAMINATION, Incorporating the Fundamentals of Neuroanatomy and Neurophysiology, by *Russell N. DeJong,* M. D. 2d edition. 1,078 pages; 368 illustrations. Paul B. Hoeber, Inc., New York, N. Y., 1958. Price $20.

TO WORK IN THE VINEYARD OF SURGERY, The Reminiscences of J. Collins Warren (1842-1927), edited, with appendices, notes and comments, by *Edward D. Churchill,* M. D. 288 pages; 2 illustrations. Harvard University Press, Cambridge, Mass., 1958. Price $6.

OBSTETRICAL PRACTICE, by *Alfred C. Beck,* M. D., and *Alexander H. Rosenthal,* M. D. 7th edition. 115 pages; illustrated. The Williams & Wilkins Company, Baltimore, Md., 1958. Price $14.

EXTERNAL COLLIMATION DETECTION OF INTRACRANIAL NEOPLASIA WITH UNSTABLE NUCLIDES, by *G. M. Shy,* M. D., M. R. C. P.; *R. B. Bradley,* B. S.; and *W. B. Matthews, Jr.,* B. S.; with a chapter on Scintillation Spectrometry, by *J. E. Francis,* B. S.; *P. R. Bell,* Ph. D.; and *C. C. Harris,* M. S. 144 pages; illustrated. The Williams & Wilkins Company, Baltimore, Md., exclusive U. S. agents, 1958. Price $7.

INTRODUCTION TO PSYCHIATRIC NURSING, by *Marion E. Kalkman,* R. N., M. A., with a foreword by *Karl M. Bowman,* M. D., 2d Edition. 331 pages. McGraw-Hill Book Company, Inc., New York, New York, 1958. Price $5.95.

THERAPEUTIC EXERCISE, Volume III of Physical Medicine Library, edited by *Sidney Licht,* M. D. 36 contributors. 893 pages; illustrated. Elizabeth Licht, Publisher, New Haven, Conn., 1958. Price $16.

EMERGENCY TREATMENT AND MANAGEMENT, by *Thomas Flint, Jr.,* M. D. 2d edition. 539 pages. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $8.

NEGROES AND MEDICINE, by *Dietrich C. Reitzes.* 400 pages. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1958. Price $7.

THE ROAD TO EMOTIONAL MATURITY, by *David Abrahamsen,* M. D. 388 pages. Prentice-Hall, Inc., New York, N. Y., 1958. Price $4.95.

INTRACARDIAC PHENOMENA, In Right and Left Heart Catheterization, by *Aldo A. Luisada,* M. D., and *Chi Kong Liu,* M. D. A 2d edition, revised and enlarged, of CARDIAC PRESSURES AND PULSES. 179 pages; illustrated. Grune and Stratton, Inc., New York, N. Y., 1958. Price $9.50.

IDEALS IN MEDICINE, A Christian Approach to Medical Practice, edited by *Vincent Edmunds,* M. D., M. R. C. P., and *C. Gordon Scorer,* M. B. E., M. D., F. R. C. S. 192 pages. The Christian Medical Society, Chicago, Ill., 1958. Price $3.

MODERN TRENDS IN ANESTHESIA, edited by *Frankis T. Evans,* M. B., B. S., F. F. A. R. C. S., D. A., and *T. Cecil Gray.* 22 contributors. 331 pages; illustrated. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, N. Y., 1958. Price $15.

PHYSIOLOGY OF PREMATURITY, Transactions of the Second Conference March 25, 26, and 27, 1957, Princeton, N. J. Edited by *Jonathan T. Lanman,* M. D. 160 pages; illustrated. Josiah Macy, Jr. Foundation, New York, N. Y., 1958. Price $3.75.

ADMINISTRATIVE MEDICINE, Transactions of the Fifth Conference October 28, 29, and 30, 1956, Princeton, N. J. Edited by *George S. Stevenson,* M. D. 197 pages. Josiah Macy, Jr. Foundation, New York, N. Y., 1958. Price $3.75.

LUMBAR DISC LESIONS, Pathogenesis and Treatment of Low Back Pain and Sciatica, by *J. R. Armstrong,* M. D., M. Ch., F. R. C. S., with a foreword by *H. Osmond-Clarke,* C. B. E., F. R. C. S. 2d edition. 244 pages; illustrated. The Williams & Wilkins Co., Baltimore, Md., 1958. Price $12.

THE PRACTICAL USE OF THE MICROSCOPE, Including Photomicrography, by *George Herbert Needham,* M. S., F. R. M. S. 493 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $15.50.

THE NEW CHEMOTHERAPY IN MENTAL ILLNESS, The History, Pharmacology and Clinical Experiences with Rauwolfia, Phenothiazine, Azacyclonol, Mephenesin, Hydroxyzine and Benactyzine Preparations, edited by *Hirsch L. Gordon,* M. D., Ph. D., F. A. P. A. 762 pages; illustrated. Philosophical Library, New York, N. Y., 1958. Price $12.

A TEXT-BOOK OF X-RAY DIAGNOSIS, by British Authors in Four Volumes. Volume III. Edited by *S. Cochrane Shanks,* C. B. E., M. D., F. R. C. P., F. F. R., and *Peter Kerley,* C. V. O., C. B. E., M. D., F. R. C. P., F. F. R., D. M. R. E. 3d edition. 883 pages; 802 illustrations. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $23.

SURGERY AND SURGICAL NURSING, by *Edward S. Stafford,* B. A., M. D., F. A. C. S., and *Doris Diller,* B. A., M. A., R. N. 3d edition. 469 pages; illustrated with 174 figures. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $5.

PERSONNEL PROGRAM GUIDE, For Nursing Education and Nursing Service Agencies, by *Ruth V. Johnston,* Ph. D. 137 pages. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $2.75.

CALLANDER'S SURGICAL ANATOMY, by *Barry J. Anson,* M. A., Ph. D., and *Walter G. Maddock,* M. S., M. D., F. A. C. S. 4th Edition. 1,157 pages; with 1,047 illustrations. W. B. Saunders Company, Philadelphia, Pa., 1958. Price $21.

DISEASES OF THE LIVER AND BILIARY SYSTEM, by *Sheila Sherlock,* M. D., F. R. C. P., M. R. C. P. 2d edition. 719 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $11.50.

A SYNOPSIS OF SURGICAL ANATOMY, by *Alexander Lee McGregor,* M. Ch., F. R. C. S., with a foreword by Sir *Harold J. Stiles,* K. B. E., F. R. C. S., 8th edition. 808 pages; 766 illustrations by Dr. *E. A. Thomas.* The Williams & Wilkins Company, Baltimore, Md., 1957. Price $7.

BASIC CARDIOLOGY, by *T. E. Gumpert,* M. B., Ch. B., F. R. C. P. 169 pages; illustrated. The Williams & Wilkins Co., Baltimore, Md., 1958. Price $6.

HEMOPHILIC ARTHROPATHIES, by *Henry H. Jordan,* M. D. 255 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $8.50.

TEXTBOOK OF MICROBIOLOGY, by *Kenneth L. Burdon,* Ph. B., Sc. M., Ph. D. 4th edition. 645 pages; illustrated. The Macmillan Company, New York, N. Y., 1958. Price $5.75.

THE GANG, A Study in Adolescent Behavior, by *Herbert A. Bloch* and *Arthur Niederhoffer.* 231 pages. Philosophical Library, New York, N. Y., 1958. Price $6.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, Volume 71, Art. 5, pages 479-806, July 30, 1958, editor-in-chief *Otto V. St. Whitelock.* "New Steroid Compounds with Progestational Activity." Consulting Editor: *Abraham E. Rakoff.* 327 pages; illustrated. The New York Academy of Sciences, New York, N. Y., 1958.

1958 IMMUNIZATION INFORMATION FOR INTERNATIONAL TRAVEL. Public Service Publication No. 384. Revised June 1958. Prepared by the Epidemiology and Immunization Branch, Division of Foreign Quarantine of the Bureau of Medical Services, United States Public Health Service. Published by Public Health Service, U. S. Department of Health, Education, and Welfare. 71 pages. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1958. Price $0.30.

HEARING THERAPY for CHILDREN, by *Alice Streng,* M. A.; *Waring J. Fitch,* M. A.; *LeRoy D. Hedgecock,* Ph. D.; *James W. Philips,* M. D.; and *James A. Carrell,* Ph. D. 2d revised edition, 353 pages; illustrated. Grune & Stratton, Inc., New York, N. Y., 1958. Price $6.75.

A SKEPTICAL PSYCHOANALYST, by *Kenneth Mark Colby,* M. D. 145 pages. The Ronald Press Company, New York, N. Y., 1958. Price $3.75.

AN ATLAS OF ESOPHAGEAL MOTILITY, in Health and Disease, by *Charles F. Code,* M. D., Ph. D.; *Brian Creamer,* M. D., M. R. C. P.; *Jerry F. Schlegel,* B. S.; *Arthur M. Olsen,* M. D., M. S. in Medicine; *F. Edmund Donoghue,* M. D., M. S. in Medicine; and *Howard A. Anderson,* M. D., M. S. in Medicine. 134 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $8.50.

CIRCULATION, edited by *John McMichael,* M. D., F. R. C. P., F. R. S. 503 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $10.50.

CLINICAL ENDOCRINOLOGY, by *Karl E. Paschkis,* M. D.; *Abraham E. Rakoff,* M. D.; and *Abraham Cantarow,* M. D. 941 pages; illustrated. Paul B. Hoeber, Inc., New York, N. Y., 1958. Price $18.

CLINICAL RADIOLOGY OF ACUTE ABDOMINAL DISORDERS, by *Bernard S. Epstein,* M. D. 352 pages; illustrated. Lea & Febiger, Philadelphia, Pa., 1958. Price $15.

THE CERVICAL SYNDROME, by *Ruth Jackson,* M. D., F. A. C. S. 2d edition. 197 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $6.50.

THIRST, by *A. V. Wolf,* Ph. D. 536 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $12.50.

MEDICINE AND THE NAVY, 1200-1900, by *J. J. Keevil,* D. S. O., R. N. Volume II, 1649-1714. 332 pages; illustrated. E. & S. Livingstone, Ltd., Edinburgh and London, Publishers, 1958. Distributed by The Williams & Wilkins Company, Baltimore, Md., 1958. Price $8.50.

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